Draft Comparative Effectiveness Review

Number xx

Medical Therapies for Children with Autism Spectrum Disorder—An Update

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. [redacted for peer review]

Prepared by:
[redacted for peer review]

Investigators:
[redacted for peer review]

AHRQ Publication No. xx-EHCxxx
<Month Year>

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Suggested citation:

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Andrew Bindman, M.D.
Director
Agency for Healthcare Research and Quality

Arlene Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Laura Pincock, Pharm.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elisabeth Kato, M.D., M.R.P.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: [redacted for peer review].

Key Informants

[redacted for peer review]

Technical Expert Panel

[redacted for peer review]

Peer Reviewers

[redacted for peer review]

Medical Therapies for Children with Autism Spectrum Disorder—An Update

Structured Abstract

Objectives. To evaluate the comparative effectiveness and safety of medical interventions (defined broadly as interventions involving the administration of external substances to the body or use of external, non-behavioral procedures to treat symptoms of ASD) for children with Autism Spectrum Disorder (ASD).

Data sources. We searched MEDLINE, EMBASE, the Cumulative Index of Nursing and Allied Health Literature, and PsycInfo from January 2010-November 2015.

Review methods. We included comparative studies of medical interventions that included at least 10 children with ASD between 2 and 12 years old. Two investigators independently screened studies and rated risk of bias. We extracted and summarized data qualitatively given significant heterogeneity. We also assessed strength of the evidence (SOE) and considered cumulative data from eligible studies included in our 2011 review of medical therapies and newly published studies.

Results. We identified 60 unique comparative studies (including13 comparative studies addressed in the 2011 review). These studies included57 randomized controlled trials [RCTs], 1 nonrandomized trial, 2 retrospective cohort studies. Thirty-three studies had low, 22 had moderate, and five had high risk of bias. Populations, treatment approaches, and outcomes assessed varied across studies. Relative to placebo, five studies addressing risperidone and aripiprazole reported significant improvements in challenging behavior in the short term (<6 months) but also significant harms including weight gain, appetite changes, and extrapyramidal symptoms. Longer term effectiveness was reported in uncontrolled extensions. Two small studies comparing risperidone and aripiprazole reported no significant differences and effects or weight gain between agents. Two RCTs addressing methylphenidate reported significant improvements in hyperactivity in children treated with medium to high doses compared with placebo, with frequent harms. Two RCTs of atomoxetine reported improvements in hyperactivity in children with ASD and Attention Deficit Hyperactivity Disorder with moderate adverse effects. Despite the number of RCTs with low or moderate risk of bias addressing nutritional supplements or specialized diets, evidence is insufficient for all clinical efficacy and harms outcomes because few, small, underpowered studies addressed each diet or supplement. Similarly, though 13 RCTs with low or moderate risk of bias compared risperidone plus an adjunct medication with risperidone plus placebo, few addressed the same adjunct agents; thus, studies provide little evidence to inform treatment decisions and can be considered primarily as pilot efficacy trials. Studies of hyperbaric oxygen therapy versus sham treatment using differing protocols reported conflicting results. Sixteen studies addressed other interventions, most evaluated in only one study, and typically reported some positive treatment effects on sleep, ASD symptoms, or language. Heterogeneity among the studies and small sample sizes precluded firm conclusions.

Conclusions. Risperidone and aripiprazole ameliorated challenging behaviors in the short term, but with significant side effects (high SOE). Methylphenidate and atomoxetine were also associated with improvements in hyperactivity in small, short-term RCTs (low SOE). Methylphenidate was associated with significant harms (low SOE) while atomoxetine was associated with moderate harms (low SOE).Omega-3 fatty acid supplementation was not associated with improvements in challenging behaviors (low SOE). Some positive effects were reported with other agents studied (risperidone adjuncts, N-Acetylcysteine, melatonin), but few studies addressed the same agent or outcomes (insufficient SOE). Data on longer term (> 6 months) results and harms of interventions are lacking. Similarly, more research is needed to understand characteristics of the child or treatment that modify outcomes and whether effectiveness of interventions generalizes across different settings such as the home or school. Current evidence also does not inform our understanding of components of interventions that may drive effects. Some therapies hold promise and warrant further study, and the conduct of studies has improved considerably over time (i.e., growing number of randomized controlled trials and use of standardized measures). However, additional studies with larger, well-characterized populations, conducted over longer time frames, and that utilize transparent and rigorous methods to permit comparison across studies, would further inform decisionmaking.

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Executive Summary

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder broadly defined by impaired social communication as well as restricted or repetitive patterns of behavior and interest. As defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition (DSM-5), specific features of ASD include deficits in social and emotional reciprocity (e.g., atypical social approaches, conversational impairment, atypical sharing of interests, attention, and affect); deficits in nonverbal communication (e.g., poorly integrated verbal and nonverbal communication, atypical body-language and gesture use, deficits in use and understanding of nonverbal communication), and deficits in maintaining appropriate relationships (e.g., challenges with peer interest, vulnerabilities forming friendships, difficulties adjusting behavior to suit social contexts) as well as restricted and repetitive patterns of behavior such as stereotyped speech, motor movements, or use of objects; excessive adherence to routine or insistence on sameness; intense interest patterns; and atypical sensory interests or responses. Symptoms of the disorder impair and limit everyday functioning and are thought to be evident in early childhood; although they may not be fully evident until later ages. Although not a core symptom, many children with ASD may also have significant cognitive impairment.

Treatment of ASD

The manifestation and severity of symptoms of ASD differ widely, and treatments include a range of behavioral, psychosocial, educational, medical, and complementary approaches[1-4] that vary by a child's age and developmental status. The goals of treatment for ASD typically focus on improving core deficits in communication, social interactions, or restricted behaviors, as changing these fundamental deficits may help children develop greater functional skills and independence.[5] Treatment frequently is complicated by symptoms or comorbidities that may warrant targeted intervention. Individual goals for treatment vary for different children and may include combinations of behavioral therapies, educational therapies, medical and related therapies, approaches targeting sensory issues, and allied health therapies; parents may also pursue complementary and alternative medicine therapies.

The antipsychotics risperidone (Risperdal) and aripiprazole (Abilify) have been specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of irritability and challenging behaviors in ASD. Many other medications are used off –label to manage behavioral symptoms such as anxiety and hyperactivity. In addition, devices such as hyperbaric oxygen chambers may be used to treat symptoms of ASD.

Scope and Key Questions (KQs)

Scope and Uses of the Review

This review updates findings reported in the 2011 AHRQ review Therapies for Children with ASD[6] with a focus on studies of medical interventions. We defined medical interventions broadly as interventions involving the administration of external substances to the body or use of external, non-behavioral procedures to treat symptoms of ASD, which includes pharmacologic agents, diet therapies, vitamins and supplements, chelating agents, electroconvulsive therapy, transcranial magnetic stimulation and hyperbaric oxygen, among other modalities. We used this

broad definition, developed with input from our clinical experts, in order to capture the landscape of medically-related interventions used to treat children with ASD. A companion review updating findings related to interventions targeting sensory challenges is available on the AHRQ Effective Health Care web site.

We anticipate that the report will be of value to clinicians who treat children with ASD, who can use the report to assess the evidence for different treatment strategies, and to federal agencies and organizations that focus on ASD or child health and who may use the report to compare treatments and determine priorities for funding. It will be of interest to families affected by ASD because of the recurring need for families and their health care providers to make the best possible decisions among numerous options. We also anticipate it will be of use to private sector organizations concerned with ASD; the report can inform such organizations' understanding of the effectiveness of treatments and the amount and quality of evidence available. Researchers can obtain a concise analysis of the current state of knowledge related to medical interventions for ASD as well as information about research gaps and needs for future research.

Key Questions

We developed KQs in consultation with Key Informants and the Task Order Officer. KQs were posted for review to the AHRQ Effective Health Care website.

KQs were as follows:

KQ1: Among children ages 2-12 with ASD, what is the comparative effectiveness (benefits and harms) of medical treatments?

a) What are the effects on core symptoms (e.g., deficits in social communication and interaction; restricted, repetitive patterns of behavior, interests, or activities including hyper- or hypo- reactivity to sensory input or unusual interest in sensory aspects of the environment) in the short term (≤6 months)?

b) What are the effects on commonly associated symptoms (e.g., motor, medical, mood/anxiety, irritability, and hyperactivity) in the short term (≤6 months)?

c) What are the longer-term effects (>6 months) on core symptoms (e.g., social deficits, communication deficits, and repetitive behaviors)?

d) What are the longer-term effects (>6 months) on commonly associated symptoms (e.g., motor, medical, mood/anxiety, irritability, and hyperactivity)?

KQ2: Among children ages 2-12 with ASD, what are the modifiers of outcome for different medical treatments?

a) Is the effectiveness of the therapies reviewed affected by the frequency, duration, intensity, or dose of the intervention?

b) Is the effectiveness of the therapies reviewed affected by co-interventions or prior treatment or the training and/or experience of the individual providing the therapy?

c) What characteristics (e.g., age, symptom severity), if any, of the child modify the effectiveness of the therapies reviewed?

d) What characteristics, if any, of the family modify the effectiveness of the therapies reviewed?

KQ3: What is the time to effect of medical interventions?

KQ4: What is the evidence that effects measured at the end of the treatment phase predict long-term functional outcomes of medical interventions?

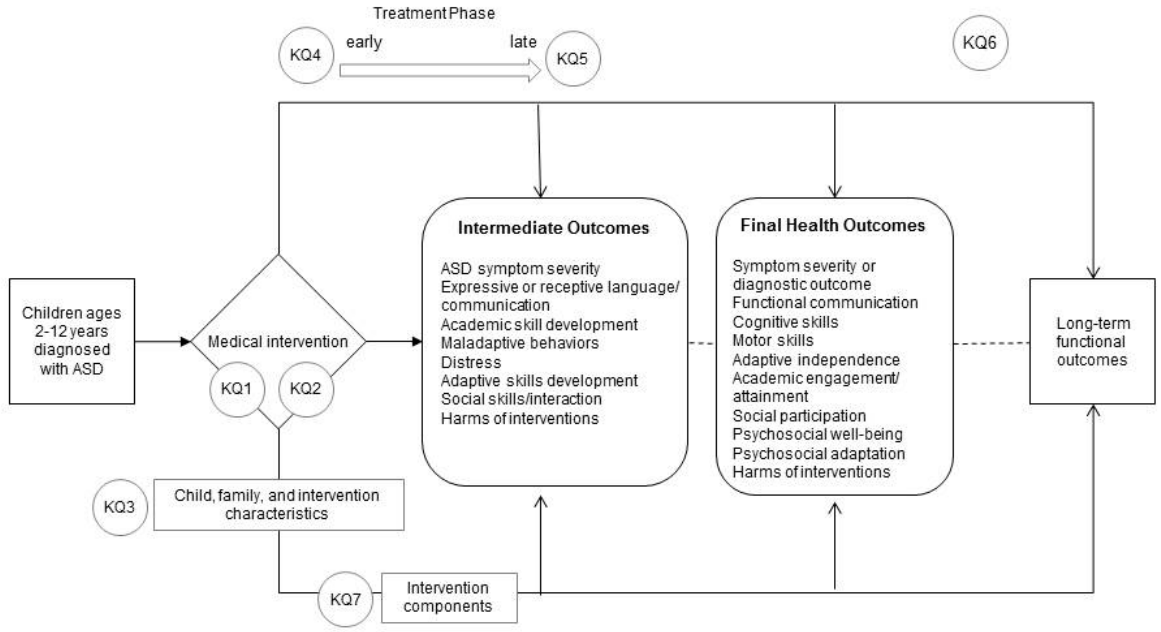
KQ5: Is the effectiveness of medical interventions maintained across environments or contexts (e.g., people, places, materials)?

KQ6: What evidence supports specific components of treatment with medical interventions as driving outcomes, either within a single treatment or across treatments?

Analytic Framework

The analytic framework illustrates the population, interventions, and outcomes that guided the literature search and synthesis. The framework depicts the KQs within the context of population, intervention, comparator, outcomes, timing, and setting (PICOTS) parameters. In general, the figures illustrate how treatment choices may result in outcomes such as changes in ASD severity, language, or cognitive skills. Outcomes may be affected by characteristics related to the child, intervention, or family.

Figure ES-1. Analytic framework



ASD=autism spectrum disorder; KQ=Key Question

Methods

Topic Surveillance

The topic for a 2011 report on therapies for children with ASD[6] was nominated by Autism Speaks in a public process using the Effective Health Care website. AHRQ published an update addressing behavioral interventions in 2014.[7] We conducted a surveillance precess to assess the need to update the earlier report by contacting topic experts about the relevance of the KQs and

new evidence that may address them. In consultation with clinical experts and stakeholders, and based on our preliminary scan of the literature and surveillance findings, we focused the review update on medical approaches and approaches to address sensory challenges (reported in a separate update). These areas reflect both areas of clinical relevance and sufficient newly published literature for a review update.

Literature Search Strategy

To ensure comprehensive retrieval of relevant studies of medical therapies for children with ASD, we used four key databases: the MEDLINE® medical literature database via the PubMed® interface; EMBASE (Excerpta Medica Database), an international biomedical and pharmacological literature database via the Ovid® interface; the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PsycINFO®. Search strategies applied a combination of controlled terms and. We conducted searches in November 2015 and will update searches while the report is undergoing peer review.

We carried out hand searches of the reference lists of recent systematic reviews or meta-analyses of studies addressing therapies for ASD. The investigative team also scanned the reference lists of studies included after the full-text review phase for additional studies that potentially could meet our inclusion criteria.

Inclusion Criteria

Table A lists the inclusion criteria we used based on our understanding of the literature, key informant and public comment during the topic refinement phase, input from the TEP, and established principles of systematic review methods.

Table A. Inclusion criteria

Category	Criteria
Study population	Children ages 2-12 with ASD (mean age plus standard deviation is ≤ 12 years and 11 months)
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs Randomized controlled trials, prospective and retrospective cohort studies with comparison groups, and nonrandomized controlled trials Other criteria Original research studies published from 2010—present and not addressed in prior reviews Studies must have relevant population and ≥20 participants with ASD (non-RCTs) or at least 10 total participants (RCTs) Studies must address one or more of the following for ASD: -Outcomes of interest -Treatment modality of interest -Predictors or drivers of treatment outcomes (e.g., biomarkers, clinical changes) -Maintenance of outcomes across environments or contexts -Sufficiently detailed methods and results to enable data extraction -Reporting of outcome data by target population or intervention

ASD=Autism Spectrum Disorder; RCT=randomized controlled trial

Study Selection

Two reviewers independently assessed each abstract and the full text of studies proceeding to full text review. A senior reviewer adjudicated disagreements in full text review .

Data Extraction and Synthesis

Data were initially extracted by one team member and reviewed for accuracy by a second.

We summarized data for KQs qualitatively using summary tables as studies were too heterogeneous to allow for meta-analyses.

Risk-of-Bias Assessment of Individual Studies

We evaluated the overall methodologic risk of bias of individual studies using the ASD-specific assessment approach developed and used in our prior reviews of interventions for ASD and informed by the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[8] Two senior investigators assessed each included study independently with disagreements resolved through discussion. Appendix D of the main report includes ratings for each study.

Strength of the Body of Evidence

Two senior investigators graded the strength of the evidence (SOE) for key intervention/outcome pairs using methods based on the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[8] We assessed the domains of study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown), directness (direct, indirect), precision (precise, imprecise), and reporting bias (detected, unsuspected). The full team reviewed the final SOE designations. The possible grades were:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.[9]

Applicability

We assessed the applicability of findings reported in the included literature addressing our KQs to the general population of children with ASD by determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category. We anticipated that areas in which applicability would be especially important to describe would include ASD severity, comorbidities, age at treatment, and intervention characteristics such provider, dosing/intensity, and setting. Applicability tables for each KQ are in Appendix G of the full report.

Results

We identified 4361 nonduplicative titles or abstracts with potential relevance, with 437 proceeding to full text review. We excluded 373 studies at full text review. We included 52 unique studies (64 publications) in the review. In addition to these 52 studies published since the completion of our original review of therapies for children with Autism Spectrum Disorder (ASD) in 2011, we include 13 comparative studies addressed in the 2011 review that also addressed an agent used in the current review. Five studies included in the 2011 review now include followup analyses published since the completion of that report; thus we describe a total of 60 studies in the review.

The 60 studies included in the review comprised 57 RCTs, one nonrandomized trial, and two retrospective cohort studies. We considered 33 studies to have low risk of bias, 22 to have moderate, and five to have high risk. Despite the high number of low and moderate risk of bias studies, few studies addressed the same interventions or outcomes, and most studies included few participants, evaluated only in the short term (< 6 months); thus, evidence for many agents remains insufficient. Because few studies addressed sub-questions under Key Questions (KQ) 1 and 2, we present results in the aggregate under each of these KQ.

KQ1. Benefits and Harms of Medical Treatments

Antipsychotics. We identified eight unique RCTs and one retrospective cohort study addressing antipsychotics (n=1053 children). Four RCTs (2 with low and 2 with moderate risk of bias) addressing risperidone reported statistically significant improvements in measures of irritability and other challenging behaviors in the treatment group compared with placebo in the short-term (≤ 6 months), with continued positive effects over a mean 21-month treatment period in an uncontrolled extension study. Side effects including somnolence and weight gain were significant. One RCT comparing risperidone plus parent training (low risk of bias) reported significant improvements in irritability, hyperactivity, and repetitive behavior in children receiving combined therapy compared with risperidone alone.

Two RCTs of aripiprazole (low risk of bias) reported significant improvements in irritability and challenging behavior in the treatment groups compared with placebo over 8 weeks of treatment and maintenance of improvements in a 52-week uncontrolled extension. Harms, including weight gain, appetite changes, lethargy, and extrapyramidal symptoms, were also significant. Another RCT (low risk of bias) reported no differences in time to relapse (return of significant negative symptoms) between children taking aripiprazole versus placebo; quality of life measures also did not differ between groups.

Two small studies with low and moderate risk of bias comparing risperidone and aripiprazole reported no significant differences in effects on challenging behaviors or general improvement; one study noted no significant differences in weight gain associated with each agent.

Stimulants. We identified three low risk of bias RCTs addressing the stimulant medications methylphenidate and guanfacine (n=152 children). Both RCTs addressing methylphenidate reported significant improvements in hyperactivity in children treated with medium to high doses compared with placebo. One RCT also noted significant treatment effects on inattention. These two small RCTs also reported on changes in social communication with inconsistent results (significant improvements over placebo in one crossover RCT and no group differences in another). Harms were frequent and included challenging behavior, anxiety, and appetite changes.

Both RCTs had short-term (<6 months) followup and few participants. One small RCT of guanfacine reported significant improvements in hyperactivity in treated participants compared with the placebo group and no significant group differences in measures of cognitive skills. Harms included behavior changes and drowsiness.

Atomoxetine. Two RCTs with low and moderate risk of bias addressed the norepinephrine reuptake inhibitor atomoxetine (n=113 children). Both reported significant treatment-related improvements in hyperactivity compared with placebo that were subsequently maintained over 20 weeks of open label, uncontrolled treatment in one RCT; inattention was significantly improved in one RCT, and side effects were generally moderate.

Diet and nutritional supplements. Fourteen RCTs evaluated the use of supplements or dietary manipulation to treat ASD symptoms and included a total of 669 children. Studies addressed nutritional supplements including omega-3 long-chain free fatty acid (FFA) supplementation, methyl-B12 supplement, digestive enzymes, L-carnitine, and the amino acid derivative N,N-Dimethylglycine. Dietary interventions addressed in studies included gluten-free and casein-free (GFCF) diet, gluten/casein challenge foods, and camels' milk. Three RCTs of omega-3 FFA versus placebo (low and moderate risk of bias) reported no significant group differences on most measures of challenging behavior, communication, language, and adaptive behavior. Two RCTs with moderate risk of bias addressed digestive enzyme supplements compared with placebo; one reported no significant treatment effects while the other reported improvements in symptom severity associated with the enzyme versus placebo. Two studies of methyl B12 and N,N-Dymethylglycine (moderate and high risk of bias) supplementation reported few significant group differences in measures of behavior or communication assessed.

Two RCTs (low and moderate risk of bias) compared GFCF diets to either an unaltered diet or a diet that contained gluten and dairy reported few differences in behavioral measures between children on restricted or unrestricted diets. Two RCTs evaluating "challenges" of gluten or casein containing foods study reported no significant group differences in measures of challenging behavior, while a high risk of bias evaluating antioxidant-rich camel's milk reported no significant differences in ASD severity between children receiving boiled or raw camel's milk or cow's milk.

Risperidone adjuncts. Thirteen placebo-controlled RCTs compared risperidone plus an adjunct medication with risperidone plus placebo (n=515). Study medications added to risperidone included celecoxib, *Ginkgo biloba*, memantine, topiramate, riluzole, buspirone, N-acetylcysteine (addressed in 2 studies), amantadine, pioglitazone, pentoxifylline, galantamine, and piracetam. All studies except one of *gingko biloba* added to risperidone reported significant improvements in irritability measured on the Aberrant Behavior Checklist (ABC) in the adjunct groups compared with placebo plus risperidone; one study of piracetam reporting only total ABC scores reported significant improvements in the adjunct group compared with placebo. Harms typically did not differ between groups.

Hyperbaric Oxygen Therapy (HBOT). Three RCTs with low and moderate risk of bias compared HBOT with a sham treatment (n=150 children). Two studies of 80 or 20 hourly treatments reported no significant differences between groups on measures of symptom severity, language, and adaptive behavior. A third (evaluating 40 HBOT or sham sessions) reported

significant improvements in overall Clinical Global Impression scores and communication and sensory measures in the treatment group compared with placebo. Studies noted that no significant harms occurred.

Other medical interventions. We categorized studies as "other" if we could not assess strength of evidence for interventions and outcomes reported (i.e., insufficient strength of evidence) and the studies did not fall under a broader category of intervention such as diet or nutritional supplements. Sixteen studies (14 RCTs, 1 nonrandomized trial, and 1 retrospective cohort study) addressed other interventions and included a total of 778 children. Most agents or interventions were addressed in only one study.

Two RCTs (low and moderate risk of bias) evaluated melatonin and reported significant improvements in sleep duration in children receiving combined behavioral therapy and melatonin compared with melatonin alone in one RCT and improvements in time to fall asleep and sleep time with melatonin versus placebo in another. Two RCTs (moderate risk of bias) of donepezil assessed differing outcomes and reported no effects on executive function and treatment-associated improvements in language. Two RCTs evaluated the diuretic bumetanide, one combining it with behavioral treatment and reported short-term positive effects on symptom severity.

Among agents evaluated in single studies, one RCT (low risk of bias) of citalopram reported no significant effects on repetitive behavior and some positive effects on challenging behaviors compared with placebo. Another RCT (low risk of bias) comparing of N-Acetylcysteine with placebo reported significant improvement in irritability in treated children as compared with the placebo group. Another moderate risk of bias RCT of amantadine reported no significant effect of daily amantadine on parent-rated behavior scores and clinician-rated CGI-Improvement compared with placebo; however, children in the amantadine arm improved significantly more than those receiving placebo in clinician-rated hyperactivity and inappropriate speech. In another RCT (low risk of bias), children receiving divalproex had greater improvements in irritability, but scores on measures of aggression and repetitive behavior did not differ between groups. Children receiving tetrahydrobiopterin in another low risk of bias RCT did not improve significantly compared with a placebo group on overall measures but improved significantly on measures of challenging and adaptive behavior.

One retrospective cohort study (high risk of bias) reported that children receiving prednisolone had significant improvements in language compared with those receiving no steroids. One RCT of oxytocin and one of mecamylamine (moderate and low risk of bias) each reported no significant treatment effects. Finally, a high risk of bias RCT comparing stem cell transplantation plus behavioral treatment, umbilical cord blood cell transplantation plus behavioral treatment, and behavioral treatment alone Symptom severity improved over time in all groups, with significantly greater improvements in the stem cell group compared with each of the other arms. An RCT of transcranial stimulation (moderate risk of bias) reported some improvements in symptom severity in the treatment group compared with a sham treatment group. Harms reported in studies comparing these interventions were diverse, and their clinical significance is difficult to determine

KQ2. Modifiers of Treatment Outcomes

While we sought modifying effects of child, provider, or intervention characteristics, few studies reported modifiers, and few were likely adequately powered to detect effects. In one

subanalysis, higher baseline irritability was associated with greater improvement in irritability than was low severity in improvement with risperidone. Greater weight gain was associated with less irritability improvement in the risperidone group. In another study of risperidone, younger age and better communication skills were associated with greater gains in communication but not with gains in daily living skills or socialization.

Studies of stimulants identified no significant phenotypic predictors of effects (e.g., baseline cognitive skills, age, IQ), but one genetic analysis identified seven genetic variations that predicted response to methylphenidate.

KQ3. Time to Effect of Interventions

While several studies reported changes in the number of children responding to a given agent over time, studies did not provide data to determine the initiation of effects.

KQ4. Evidence that Effects Measured at the End of Treatment Predict Long-Term Functional Outcomes

Few studies had longer-term followup and those with more than 6 months of treatment or followup typically did not report functional outcomes. In one study, risperidone use was not associated with changes in IQ: changes from baseline to the end of study in class assignment (e.g., special education, regular classroom) were not significant.

KQ5. Effectiveness Across Environments or Contexts

Five studies reported teacher ratings of outcome measures that provide some information to address this KQ, but the limited results preclude conclusions. One RCT of omega-3 fatty acids reported no significant group differences in teacher ratings of challenging behaviors (parents also rated few measures as improved), while another RCT of docosahexaenoic acid (DHA) supplementation versus placebo reported improvement in parent-rated social skills in children receiving placebo vs. those receiving DHA, while teachers rated communication as more improved in the treatment group compared with placebo. RCTs of methylphenidate reported general agreement between parent and teacher ratings of hyperactivity. In one RCT, both parents and teachers considered hyperactivity and impulsive behavior to be significantly improved in the treatment group compared with placebo, but teachers (vs. parents) reported no significant group differences in inattention or oppositional behavior. Finally, an RCT of atomoxetine reported significant teacher-rated improvements in hyperactivity in the atomoxetine group compared with placebo but teacher ratings of cognitive problems/inattention, oppositional behavior, or overall ADHD symptoms did not differ between groups.

KQ6. Drivers of Treatment Outcomes

We did not identify any studies that provided data to address this KQ.

Discussion

State of the Literature

We identified a total of 60 unique comparative studies, primarily (n=57) RCTs, addressing medical interventions. Most studies were small (median 40 total participants/study) and

addressed variable agents. Most studies had placebo comparators, while four compared a pharmaceutical agent to behavioral treatment or combined pharmaceutical and behavioral treatment. Studies were typically of short duration (≤ 6 months, range 4 days to 24 months), with few studies (n=3) reporting longer term followup after the immediate intervention period.

The methodologic rigor of studies has increased substantially compared with those studies reported in our 2011 review of therapies for children with Autism Spectrum Disorder (ASD).[6] However, while studies were generally well conducted, evidence remains insufficient for most interventions due to small sample sizes, lack of long term followup, and heterogeneous agents and populations.

Key Findings and Strength of Evidence

KQ1. Benefits and Harms of Medical Treatments

Antipsychotics. Studies of antipsychotics addressed either risperidone or aripiprazole and reported significant improvements in measures of challenging behavior in the short term (< 6 months) in children receiving the medications compared with those receiving placebo. Harms of these agents, including extrapyramidal symptoms and weight gain, were also significant. Studies reporting longer term followup (up to 21 months for risperidone) reported continued effectiveness in most children but did not include control groups.

We considered the strength of the evidence to be high for short-term improvements in challenging behaviors associated with risperidone and aripiprazole and high for significant harms associated with these agents (Table B). We considered the strength of evidence to be low for longer term (> 6 months) behavioral improvements associated with aripiprazole (assessed in one RCT with an uncontrolled, open-label extension) and low for longer term improvements with risperidone as only two longer-term studies assessed this agent. Other outcomes (e.g., ASD symptom severity, repetitive behavior, adaptive behavior) were addressed in single studies; thus, we considered strength of evidence insufficient for all other intervention/outcome pairs. As only two studies reported data comparing aripiprazole and risperidone, we considered the strength of the evidence for any comparison insufficient.

Stimulants. Two RCTs of methylphenidate and one of guanfacine reported improvements in hyperactivity and other challenging behaviors with treatment compared with placebo. Significant side effects were associated with methylphenidate including aggressive behavior and appetite changes. Harms reported with guanfacine included drowsiness and decreased appetite.

Strength of evidence for effects of methylphenidate on hyperactivity was low as studies were small and short term (Table B). Strength of evidence was also low for no effect on oppositional behavior and low for association with significant harms given the small sample size. Evidence was insufficient to comment on potential effects of methylphenidate on social communication. One RCT of guanfacine reported improvements in hyperactivity, impulsiveness, and attention, but strength of evidence was insufficient given the small sample size and short-term assessment (8 weeks of treatment with immediate followup).

Atomoxetine. RCTs addressing atomoxetine reported significant treatment-related improvements in hyperactivity compared with placebo that were maintained over 20 weeks of

open label, uncontrolled treatment in one study; inattention was significantly improved in one study, and side effects were generally moderate.

SOE was low for short-term positive effects of atomoxetine compared with placebo on hyperactivity (Table B). SOE for longer term effects is insufficient as only one study reported a longer duration treatment. SOE was insufficient for effects on inattention as studies reported inconsistent findings.

Nutritional supplements and dietary interventions. SOE was low for a lack of effect of omega-3 fatty acids on challenging behaviors and low for a lack of harms (Table B). Despite the number of RCTs with low or moderate risk of bias addressing other supplements or diets, evidence is insufficient to determine their effects on any outcome in the short- or long-term. Most studies were small, short-term (ranging from 1 week to 7 months, with 24 months of treatment in one study), and most (4/6; no calculation provided in 9 studies) studies reporting power calculations were not adequately powered to detect effects. SOE was insufficient for all other comparisons and outcomes addressed as few studies addressed the same agents, comparators, or outcomes.

Risperidone adjuncts. Despite the number of RCTs with low or moderate risk of bias, studies present little evidence to inform treatment decisions and can be considered primarily as pilot efficacy trials. All studies were short-term and lacked followup past the end of treatment. Studies included few participants (median 40 total/study) and few examined the same adjunct agent or outcomes besides the ABC Irritability subscale. Only two studies addressed the same outcomes with different doses of the same agent (N-acetylcysteine

SOE was insufficient to assess effects of risperidone plus adjunctive agents including amantadine, buspirone, celecoxib, memantine, riluzole, *gingko biloba*, pioglitazone, or topiramate on any outcome assessed as no study addressed the same adjunctive agent. Studies were also small (<50 children total) and short-term (8-10 weeks of treatment). While two RCTs addressed risperidone plus N-acetylcysteine, strength of evidence is insufficient to comment on effects given the small number of participants and high attrition.

Hyperbaric oxygen therapy. Three RCTs of HBOT used different doses and reported inconsistent results. We considered SOE to be insufficient to assess effects on ASD symptoms and language and low for a lack of harms (Table B).

Studies of other medical interventions. Studies of other agents were typically small and short-term, and these limitations prohibited conclusions about their findings. SOE was insufficient for all comparisons.

Table B. Summary of evidence in studies addressing medical interventions for children with ASD

Intervention and comparator	Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Risperidone vs. placebo	3 RCT (274)	Challenging behavior (<6 months)	High SOE for effectiveness in improving challenging behavior	Significant improvement in treatment group vs. placebo in 3 RCTs with 6-8 week treatment phases; improvement maintained in 2 RCTs with 6 months of treatment
	2 RCT (94)	Challenging	Low SOE for	Improvement maintained in 1 RCT

Intervention and comparator	Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
		behavior (>6 months)	effectiveness	with 6 months of treatment and in one open label extension with no comparison group with mean 21 months treatment duration
	4 RCT (298)	Harms	High SOE for significant harms associated with risperidone	Harms including weight gain, appetite changes, drowsiness, fatigue, extrapyramidal symptoms, drooling/hypersalivation, and gastrointestinal symptoms consistently reported
Aripiprazole vs. Placebo	2 RCT (316)	Challenging behavior (<6 months)	High SOE for effectiveness in improving challenging behavior	Significant improvements in 2 short-term RCTs in treatment groups
	2 RCT (415)	Challenging behavior (>6 months)	Low SOE for effectiveness in improving challenging behaviors	In longer term followup, no differences in time to relapse of symptoms between aripiprazole and placebo groups in one 16 week RCT and continued improvements in ABC in one 52-week open label continuation with no control arm
	3 RCT (415)	Harms	High SOE for significant harms associated with aripiprazole	Harms including weight gain, appetite changes, somnolence, extrapyramidal symptoms, drooling/hypersalivation, infection, and gastrointestinal symptoms consistently reported
MPH vs. placebo	2 RCT (90)	Hyperactivity	Low SOE for improvements in hyperactivity	Significant improvement with MPH compared with placebo on parent and teacher-rated measures; differential effect of dose not clear (little effect on 1 study and linear effect in another); SOE is low given small sample size and lack of long-term followup
	2 RCT (90)	Oppositional behavior	Low SOE for no effect on oppositional behavior	Significant improvement with MPH on parent-rated measure at medium dose level only in 1 RCT; no differences on teacher-rated measures. No differences in teacher-, parent-, or clinician-rated measures in another RCT
	2 RCT (90)	Harms	Low SOE for association of MPH with significant harms	Rates of children experiencing harms ranged from 0-75%; higher rates reported for repetitive behaviors or speech, loss of appetite, and irritability. Irritability responsible for withdrawals (n=6) in one RCT; SOE is low given small sample size
Atomoxetine vs. Placebo	2 RCT (113)	Hyperactivity (≤ 3 months)	Low SOE for improvements in hyperactivity in the short-term	Significant improvements in rating of hyperactivity in treatment group compared with placebo in both studies
	2 RCT (113)	Harms	Low SOE for moderate harms associated with atomoxetine	No serious adverse events reported in 2 studies; most harms attenuated over open label extension phase

Intervention and comparator	Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Omega-3 supplementation vs. Placebo	3 RCT (119)	Challenging behaviors	Low SOE for no effect	No significant differences between groups in three small, short-term RCTs
		Harms	Low SOE for minimal harms	No clinically significant harms reported in any study
Hyperbaric oxygen therapy vs. Placebo	3 RCT (150)	Harms	Low SOE for lack of significant harms associated with HBOT	No study reported harms considered clinically important

HBOT=hyperbaric oxygen therapy; MPH=methylphenidate; RCT=randomized controlled trial; SOE=strength of evidence

Other Key Questions

Few studies reported modifying characteristics, and no characteristics were consistent modifiers. Few studies reported data to assess time to effect of interventions. One study assessing transcranial stimulation reported changes in peak alpha frequency immediately post-treatment in children receiving active versus sham stimulation (significant change from baseline in active treatment group and significant between group differences at some electrode sites), but the clinical effects of such changes are not clear.[10, 11]

Few studies had longer-term followup and those few with 6 months or more of treatment or followup typically did not report functional outcomes; thus our understanding of whether effects at the end of treatment predict functional outcomes. Four studies reported teacher ratings of outcome measures that provide some information to address effectiveness of treatments across environments or contexts, but the limited results preclude conclusions. Finally, we did not identify studies that provided data to address drivers of treatment outcomes.

Applicability

Study participants were generally recruited from specialty clinical service programs and represent non-primary care populations. As such, families of these children may be seeking a higher level of care than those of the broader population of children with ASD based upon more severe or acute symptoms, including aggression or other challenging behaviors. Most studies of medical interventions targeted elementary school aged and older children with autism, with little data on the treatment of younger children. Most studies included majority male populations (consistent with the male prevalence of ASD).

Studies also included children with highly variable severity of challenging behaviors, ASD symptom severity, and cognitive impairment. Studies of pharmacological agents often sampled children with high levels of specific symptom patterns (e.g., children with severe challenging behavior at baseline where parents may be willing to pursue pharmacologic intervention and trial participation) who may not reflect the wider population of children with ASD in whom these challenges may not be present. Most of the studies reported including children with at least moderate level of severity of ASD. Studies of stimulants included children with cognitive impairment and with comorbidities including attention deficit hyperactivity disorder, oppositional defiant disorder, and obsessive compulsive disorder. Studies of other approaches had similarly heterogeneous populations. Dietary and nutritional studies included some younger children, with severity of autism not well described or the degree of intellectual functioning not well characterized in most studies. This heterogeneity in population characteristics limits the

generalizability of findings to children with differing levels of symptom expression or comorbidities.

Studies addressed a variety of agents and typically reported use of concurrent medications or other therapies. Most agents studied are accessible in the United States albeit with few receiving FDA approval for use. ,. Comparators among non-placebo controlled studies varied, and few studies assessed the effect of concomitant behavioral or other therapies, though many children with ASD receive multiple interventions. The treatments studied may not adequately reflect the broad range of treatment combinations used in the general population of children with ASD. .

As noted, few studies evaluated longer term treatment (> 6 months); short treatment and followup periods limit our ability to understand potential longer term outcomes such as academic achievement or longer term harms.

Overall, given the heterogeneity of these studies, and the heterogeneity of children with ASD, it is difficult to generalize findings to the overall population of individuals with ASD. These limitations to generalizability likely reflect both the significant heterogeneity of ASD itself as well as its associated features, such as irritability. Thus, while there is a growing evidence base for treating certain symptoms in certain populations, these findings underscore the continued need for individualized treatment approaches that are informed by the emerging evidence base for benefits as well as harms of medical intervention, with careful consideration of patient symptom presentation and functioning level relative to study populations and applicability of the known literature.

Limitations of the Comparative Effectiveness Review Process

We included studies published in English only and did not include unpublished data. We scanned a random sample of 150 non-English abstracts retrieved by our MEDLINE search. Most studies appeared to be case series, narrative reviews, basic science studies, or studies assessing etiology. Only two studies appeared to meet inclusion criteria; thus, given the high percentage of ineligible items in this scan (99%), we concluded that excluding non-English studies would not introduce significant bias into the review. We also included only comparative studies of medical interventions and including at least 10 children with ASD. Given heterogeneity in treatment regimens, outcomes addressed in each study, and patient populations, we were limited in our ability to meta-analyze findings or identify potential subgroups that may respond more favorably to specific treatments. Finally, we used a non-validated tool to assess risk of bias, though we note that the tool evaluates similar constructs to those assessed in tools such as that used by the Cochrane Collaboration, with the addition of ASD-specific domains.

Limitations of the Evidence Base

As noted, studies in the review had small sample sizes and typically limited duration of intervention and followup after intervention, despite significant improvements in study design and execution over time. Populations across studies were heterogeneous in terms of challenging behaviors, ASD symptom severity, age, and comorbidities. Few studies addressed the same agent and outcomes, and few assessed potential factors that may modify effectiveness or drive effects of interventions. Many (n=53) studies also explicitly noted that concomitant interventions were

held steady during the study treatment period; however, few studies reported specific analyses to control for or assess the effects of additional treatments.

Despite these limitations, investigators have made significant improvements in incorporating commonly used measures of symptom severity and behavior to facilitate comparisons across studies. Studies also typically described interventions fully, used standardized diagnostic processes and blinded assessors, and reported on the use or restriction of concomitant interventions.

Implications for Clinical and Policy Decisionmaking

This review provides some evidence for decisionmaking about medical interventions for children with ASD. The clearest evidence favors the use of the antipsychotics risperidone and aripiprazole to address challenging behaviors in the short-term (<6 months); however, clinicians and caregivers must balance the significant harms of these agents. The significant side effect profiles make it clear that although these drugs are efficacious, caution is warranted regarding their use in patients without severe impairments or risk of injury. Few studies addressed longer term effects of these agents; thus, our confidence in longer term (> 6 months) effectiveness is low. Studies of adjuncts to risperidone typically reported positive effects on challenging behaviors, but few studies addressed the same agents, precluding our ability to draw conclusions about their effectiveness.

Some evidence supports the use of methylphenidate and atomoxetine for hyperactivity, but only two small, short-term comparative studies addressed each agent, so our confidence in effects is limited. Given that many children with ASD are currently treated with medical interventions, strikingly little evidence exists to support clear benefit for most medical interventions, especially in the realm of interventions such as restrictive diets and supplements. Studies of nutritional supplements or specialized diets were typically underpowered and provided little evidence of effects of these approaches. Several agents were addressed in single studies, which limits conclusions about their effects.

Decisional dilemmas remain regarding characteristics of the child, family, or intervention that may modify effectiveness or predict which children may be most likely to benefit from a given approach. Similarly, the literature base is currently insufficient to inform our understanding of the time to effect of interventions, longer term effectiveness of interventions, generalizability of effects outside the treatment context, effectiveness and applicability to broader ASD populations, and components that may drive effectiveness.

Research Gaps and Areas for Future Research

Improving research in this area should include methodologic considerations of power and sample size and durability of effects. Sample size and participant followup were frequently insufficient to allow firm conclusions. Duration of treatment and followup were generally short (< 6 months); those studies with longer duration of treatment were open label extensions of RCTs and lacked control arms. Few studies provided data on long-term outcomes after cessation of treatment. Future studies should extend the followup period and assess the degree to which outcomes are durable in “real world” situations.

Another critical area for further research is identifying which children are likely to benefit from particular interventions. To date, studies have provided limited characterization of the subpopulation of children who experience positive response to medical interventions and limited characterization of the extent or type of behavioral challenges children experience at baseline.

Children with ASD also typically receive multiple types of therapies, but few studies addressed combinations of medical and behavioral or other categories of interventions or a medical treatment compared with a non-medical treatment. Few attempted to account for potential effects on ongoing interventions. This not only limited our ability to interpret the effects of medical treatments in isolation but represents a significant gap for families and providers in choosing additional treatments that may bolster (or impair) the effects of behavioral, medication, or other therapies. Few studies (n=9) compared active treatments, and future research to assess comparative effectiveness of antipsychotics and other medications is necessary.

In addition, much of the medical intervention literature relies on baseline and outcome measures that have specific limits in understanding individualized response. Future research attempting to elucidate potential biobehavioral markers of response may prove useful. Research in understanding outcomes of importance to patients and caregivers, such as quality of life, is also lacking.

Harms reporting varied across studies; some studies amply described how harms were tracked, while others listed harms with no indication of how they were assessed (e.g., parent recall, checklist, clinician assessment during followup). This lack of reporting makes comparing harms across studies difficult. For instance, while studies of atomoxetine generally reported fewer harms than did studies of methylphenidate in children with ADHD symptoms, exploring differences in safety profiles is an important area for additional research.

Conclusions

Risperidone and aripiprazole ameliorated challenging behaviors in the short term (< 6 months), but had significant side effects. Methylphenidate and atomoxetine were also associated with improvements in hyperactivity in small, short-term RCTs (with uncontrolled open label extensions). Data on longer term (> 6 months)results and harms of interventions are lacking. Similarly, more research is needed to understand characteristics of the child or treatment that modify outcomes and whether effectiveness of interventions generalizes across different settings such as the home or school. Current evidence also does not inform our understanding of components of interventions that may drive effects. Some therapies hold promise and warrant further study, and the conduct of studies has improved considerably over time (i.e., growing number of randomized controlled trials and use of standardized measures). However, additional studies with larger, well-characterized populations over longer time frames, and that utilize transparent and rigorous methods that permit comparison across studies, would further inform decisionmaking.

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Introduction

Background

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder broadly defined by impaired social communication as well as restricted or repetitive patterns of behavior and interest. As defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition (DSM-5), specific features of ASD include deficits in social and emotional reciprocity (e.g., atypical social approaches, conversational impairment, atypical sharing of interests, attention, and affect); deficits in nonverbal communication (e.g., poorly integrated verbal and nonverbal communication, atypical body-language and gesture use, deficits in use and understanding of nonverbal communication), and deficits in maintaining appropriate relationships (e.g., challenges with peer interest, vulnerabilities forming friendships, difficulties adjusting behavior to suit social contexts) as well as restricted and repetitive patterns of behavior such as stereotyped speech, motor movements, or use of objects; excessive adherence to routine or insistence on sameness; intense interest patterns; and atypical sensory interests or responses. Symptoms of the disorder impair and limit everyday functioning and are thought to be evident in early childhood; although they may not be fully evident until later ages. Although not a core symptom, many children with ASD may also have significant cognitive impairment.

The prevalence of ASD in the United States is 14.7 cases per 1,000 children living in the communities surveyed, or 1 in 68, with rate estimates varying widely by region of the country, sex, and race/ethnicity.[1] Considerably more males (1 in 42) than females (1 in 189) are affected. For some individuals, symptoms of ASD may improve with intervention and maturation; however, core deficits typically translate into varying developmental presentations that persist throughout the lifespan.[2]

Treatment of ASD

The manifestation and severity of symptoms of ASD differ widely, and treatments include a range of behavioral, psychosocial, educational, medical, and complementary approaches[3-6] that vary by a child's age and developmental status. The goals of treatment for ASD typically focus on improving core deficits in communication, social interactions, or restricted behaviors, as changing these fundamental deficits may help children develop greater functional skills and independence.[7] Treatment frequently is complicated by symptoms or comorbidities that may warrant targeted intervention (e.g., significant challenging behavior, attention and hyperactivity concerns, depression, anxiety). There is no cure for ASD and no global consensus on which intervention is most effective.[8, 9] Individual goals for treatment vary for different children and may include combinations of behavioral therapies, educational therapies, medical and related therapies, approaches targeting sensory issues, and allied health therapies; parents may also pursue complementary and alternative medicine therapies.

The antipsychotics risperidone (Risperdal) and aripiprazole (Abilify) have been specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of irritability and challenging behaviors in ASD. Many other medications are used off –label to manage behavioral symptoms such as anxiety and hyperactivity. In addition, devices such as hyperbaric oxygen chambers may be used to treat symptoms of ASD, though hyperbaric oxygen has not been approved by the FDA for ASD treatment.[10]

Scope and Key Questions

Scope of Review

This review updates findings reported in the 2011 Agency for Healthcare Research and Quality (AHRQ) review of Therapies for Children with ASD[11] with a focus on studies of medical interventions. We defined medical interventions broadly as interventions involving the administration of external substances to the body or use of external, non-behavioral procedures to treat symptoms of ASD, which includes pharmacologic agents, diet therapies, vitamins and supplements, chelating agents, electroconvulsive therapy, transcranial magnetic stimulation and hyperbaric oxygen, among other modalities. We used this broad definition, developed with input from our clinical experts, in order to capture the landscape of medically-related interventions used to treat children with ASD. We integrate syntheses of comparative studies evaluating medical interventions addressed in our 2011 review of therapies for children with ASD[11] if they addressed an agent evaluated in a study identified for the current review.

A companion review updating findings related to interventions targeting sensory challenges is available on the AHRQ Effective Health Care web site.

Key Questions (KQs)

We developed KQs in consultation with Key Informants and the Task Order Officer. KQs were posted for review to the AHRQ Effective Health Care website.

KQs were as follows:

KQ1: Among children ages 2-12 with ASD, what is the comparative effectiveness (benefits and harms) of medical treatments?

a) What are the effects on core symptoms (e.g., deficits in social communication and interaction; restricted, repetitive patterns of behavior, interests, or activities including hyper- or hypo- reactivity to sensory input or unusual interest in sensory aspects of the environment) in the short term (≤6 months)?

b) What are the effects on commonly associated symptoms (e.g., motor, medical, mood/anxiety, irritability, and hyperactivity) in the short term (≤6 months)?

c) What are the longer-term effects (>6 months) on core symptoms (e.g., social deficits, communication deficits, and repetitive behaviors)?

d) What are the longer-term effects (>6 months) on commonly associated symptoms (e.g., motor, medical, mood/anxiety, irritability, and hyperactivity)?

KQ2: Among children ages 2-12 with ASD, what are the modifiers of outcome for different medical treatments?

a) Is the effectiveness of the therapies reviewed affected by the frequency, duration, intensity, or dose of the intervention?

b) Is the effectiveness of the therapies reviewed affected by co-interventions or prior treatment or the training and/or experience of the individual providing the therapy?

c) What characteristics (e.g., age, symptom severity), if any, of the child modify the effectiveness of the therapies reviewed?

d) What characteristics, if any, of the family modify the effectiveness of the therapies reviewed?

KQ3: What is the time to effect of medical interventions?

KQ4: What is the evidence that effects measured at the end of the treatment phase predict long-term functional outcomes of medical interventions?

KQ5: Is the effectiveness of medical interventions maintained across environments or contexts (e.g., people, places, materials)?

KQ6: What evidence supports specific components of treatment with medical interventions as driving outcomes, either within a single treatment or across treatments?

Table 1 outlines Population, Intervention, Comparator, Outcomes, Timing, and Setting (PICOTS) characteristics for each KQ.

Table 1. PICOTS characteristics

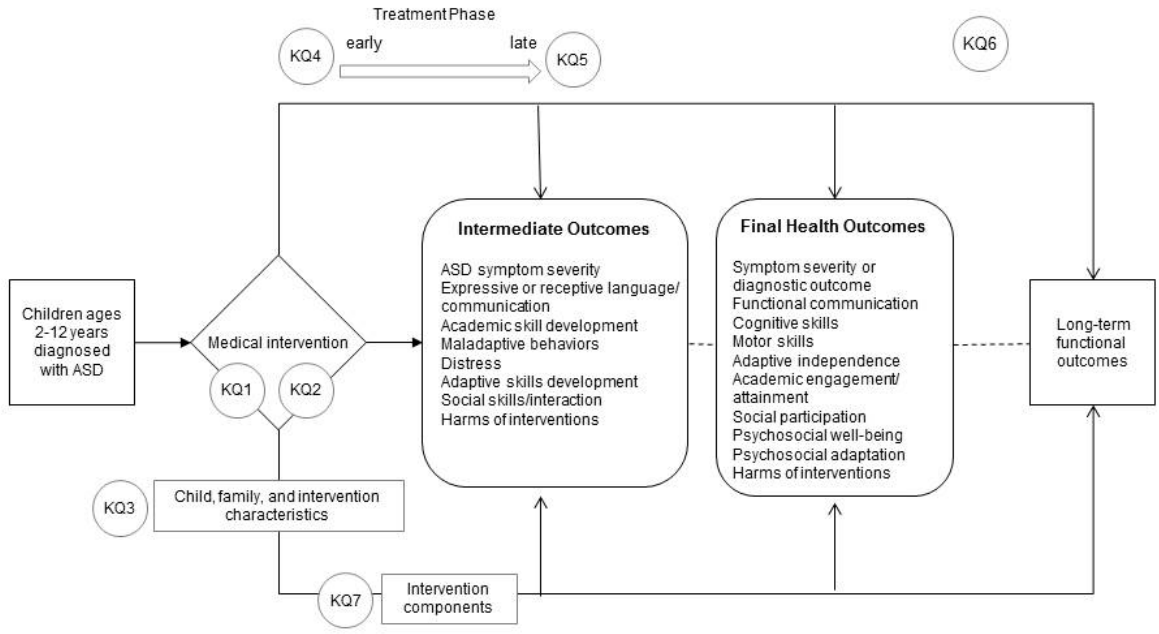
PICOTS	Criteria
Population	Children with ASD between the ages of 2 and 12 years (mean age plus standard deviation is ≤ 12 years and 11 months)
Intervention(s)	Medical interventions (pharmaceutical agents, supplements and diets, hyperbaric oxygen, etc.)
Comparator	• Inactive control (e.g., no treatment, watchful waiting, waitlist control, placebo) • Alternate intervention
Outcomes	**Intermediate outcomes** • ASD symptom severity • Expressive or receptive language/communication • Academic skill development • Maladaptive behaviors • Distress • Adaptive skills development • Social skills/interaction • Harms of interventions **Final health outcomes** • Symptom severity or diagnostic outcome • Functional communication • Cognitive skills • Motor skills • Adaptive independence • Academic engagement/attainment (e.g., mainstream school placement or integration) • Social participation • Psychosocial well-being • Psychosocial adaptation • Harms of interventions
Timing	Any (i.e., short and long term outcomes as reported in eligible study publications)
Setting	Any primary, specialty, community, or educational setting

ASD=Autism Spectrum Disorder; PICOTS=population, intervention, comparator, outcome, timing, setting

Analytic Framework

The analytic framework illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis.

Figure 1. Analytic framework



ASD=autism spectrum disorder; KQ=Key Question

Organization of This Report

The Methods section describes the review processes including search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, methods for extraction of data, and compiling evidence. We also describe our approach to grading the risk of bias of the literature and describing the strength of the body of evidence.

The Results section presents the findings of the literature search and the review of the evidence by KQ, synthesizing the findings across strategies. We present findings for each KQ organized by intervention and outcome area. Because few studies addressed sub-questions under KQ 1 and 2, we present results in the aggregate under each of these KQ.

The Discussion section of the report discusses the results and expands on methodologic considerations relevant to each KQ. We also outline the current state of the literature and challenges for future research in the field. The report includes a number of appendices to provide further detail on our methods and the studies assessed. The appendices are as follows:

- Appendix A: Search Strategies
- Appendix B: Screening and Risk of Bias Assessment Forms
- Appendix C: Excluded Studies
- Appendix D: Risk of Bias Ratings
- Appendix E: Applicability Tables
- Appendix F: Detailed Tables of Findings

Uses of This Evidence Report

We anticipate that the report will be of value to clinicians who treat children with ASD, who can use the report to assess the evidence for different treatment strategies. In addition, this

review will be of use to the National Institutes of Health, U.S. Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, and the Health Resources and Services Administration–all of which have offices or bureaus devoted to child health issues and who may use the report to compare treatments and determine priorities for funding. This report can bring practitioners up to date about the current state of evidence related to medical interventions, and it provides an assessment of the quality of studies that aim to determine the outcomes of medical options for the management of ASD. It will be of interest to families affected by ASD because of the recurring need for families and their health care providers to make the best possible decisions among numerous options. We also anticipate it will be of use to private sector organizations concerned with ASD; the report can inform such organizations' understanding of the effectiveness of treatments and the amount and quality of evidence available. Researchers can obtain a concise analysis of the current state of knowledge and future research needs related to medical interventions for ASD.

Methods

In this chapter, we document the procedures that we used to produce a comparative effectiveness review update addressing medical interventions for children with autism spectrum disorder (ASD). These procedures follow the methods outlined in the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[12]

Topic Surveillance and Review Protocol

The topic for the original report (2011[11]) was nominated by Autism Speaks in a public process using the Effective Health Care website. AHRQ published an update addressing behavioral interventions in 2014.[13] We conducted a surveillance precess to assess the need to update the report by contacting topic experts about the relevance of the Key Questions (KQs) and new evidence that may address them. All members of the research team were required to submit information about potential conflicts of interest before initiation of the work. No members of the review team had any conflicts.

In consultation with clinical experts and stakeholders, and based on our preliminary scan of the literature and surveillance findings, we focused the review update on medical approaches and approaches to address sensory challenges (reported in a separate update). These areas reflect both areas of clinical relevance and sufficient newly published literature for a review update. Based also on the surveillance process and discussions with stakeholders, we revised the Key Questions (KQs) addressed in the 2011 report[11] to reflect the focus on medical and sensory approaches specifically. We also eliminated a question on approaches for children at risk for ASD as such children are unlikely to be included in studies in the target areas for this review update.

After review from AHRQ, the questions and framework were posted online for public comment. No changes to the questions or framework were recommended. We identified technical experts on the topic to provide assistance during the project. The Technical Expert Panel (TEP), representing the fields of pediatrics and developmental pediatrics, psychiatry, family medicine, and occupational therapy and allied health, contributed to the AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included seven members serving as technical or clinical experts. To ensure robust, scientifically relevant work, TEP members participated in conference calls to:

- Help to refine the analytic framework and KQ at the beginning of the project;
- Discuss inclusion/exclusion criteria; and
- Assist with determining key interventions and outcomes of interest.

The final protocol was posted to the AHRQ Effective Health Care web site and registered in the PROSPERO international register of systematic reviews (ID#: CRD42016033941).

Literature Search Strategy

Search Strategy

To ensure comprehensive retrieval of relevant studies of medical therapies for children with ASD, we used four key databases: the MEDLINE® medical literature database via the PubMed® interface; EMBASE (Excerpta Medica Database), an international biomedical and

pharmacological literature database via the Ovid® interface; the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PsycINFO®. Search strategies for KQs applied a combination of controlled vocabulary (Medical Subject Headings [MeSH] and Emtree headings) and key words to focus specifically on medical interventions for ASD and harms of interventions (Appendix A). We restricted literature searches for KQs to studies published from 2010 to the present to reflect literature available since the publication of the 2011 review.[11] We last conducted searches in November 2015 and will update them while the report is undergoing peer review.

Gray Literature

We searched web sites of organizations likely to conduct research, issue guidance, or generate policies for ASD (e.g., Autism Speaks, the American Academy of Child and Adolescent Psychiatry) to inform the review's background and discussion sections. We searched government and regulatory agency web sites for contextual information on benefits and harms of ASD interventions. We searched ClinicalTrials.gov and other trial registries for information about relevant ongoing trials and to confirm that we have obtained available publications of results from completed trials.

Inclusion Criteria

Table 2 outlines inclusion criteria. We required that eligible randomized controlled trials [RCTs] have a total minimum sample size of 10. We required a higher minimum sample size (n=20) for other comparative studies as they typically have fewer controls for bias than RCTs.

We included studies published in English only. In the opinion of our content experts, much of the relevant literature on ASD is published in English; however, we scanned a sample of 150 non-English abstracts to gauge the number of anticipated non-English studies that would meet inclusion criteria. Two non-English studies appeared to meet our criteria. Given this small proportion of potentially eligible studies, we feel that excluding these publications is unlikely to introduce significant bias.

Eligible studies also reported one or more outcomes of interest and included children at least 2 years of age and up to and including age 12. Studies also included only children with a diagnosis of ASD (or data reported separately for children with ASD).

Table 2. Inclusion criteria

Category	Criteria
Study population	Children ages 2-12 with ASD (mean age plus standard deviation is ≤ 12 years and 11 months)
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs Randomized controlled trials, prospective and retrospective cohort studies with comparison groups, and nonrandomized controlled trials Other criteria Original research studies published from 2010—present and not addressed in prior reviews Studies must have relevant population and ≥20 participants with ASD (non-RCTs) or at least 10 total participants (RCTs) Studies must address one or more of the following for ASD: -Outcomes of interest

Category	Criteria
	-Treatment modality of interest -Predictors or drivers of treatment outcomes (e.g., biomarkers, clinical changes) -Maintenance of outcomes across environments or contexts -Sufficiently detailed methods and results to enable data extraction -Reporting of outcome data by target population or intervention

ASD=Autism Spectrum Disorder; RCT=randomized controlled trial

Study Selection

Once we identified articles through the electronic database searches and hand-searching, we examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated the abstracts of studies identified in our searches for KQs for inclusion or exclusion, using an Abstract Review Form (Appendix B). If one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it. Following abstract review, two reviewers independently assessed the full text of each included study using a standardized form (Appendix B) that included questions stemming from our inclusion and exclusion criteria. A senior reviewer resolved disagreements between reviewers.

We conducted all abstract and full text reviews using the DistillerSR online screening application (Evidence Partners Incorporated, Ottawa, Ontario). Appendix C includes a list of excluded studies and the reasons for exclusion. Data extracted for each study are available via the Systematic Review Data Repository (http://srdr.ahrq.gov/).

Data Extraction

The staff members and clinical experts (including two psychiatrists, two psychologists, and three epidemiologists/systematic reviewers) who conducted this review jointly developed the data extraction forms for the KQs. We designed forms to provide sufficient information to enable readers to understand the studies and to determine their quality; we gave particular emphasis to essential information related to the KQs. The team was trained to extract data by extracting several articles into the template and then reconvening as a group to discuss the utility of the template. We repeated this process through several iterations until we decided that the templates included the appropriate categories for gathering the information contained in the articles and for potential meta-analyses. Team data extractors shared the task of initially entering information into the evidence tables. A second team member also reviewed the articles and edited all initial entries for accuracy, completeness, and consistency. A senior reviewer reconciled disagreements concerning the information reported.

The full research team met regularly during the article extraction period and discussed issues related to the data extraction process. In addition to outcomes related to the effectiveness of treatment (e.g., changes in ASD severity), we extracted all data available on harms. Harms encompass the full range of specific negative effects, including the narrower definition of adverse events.

Data Synthesis

We summarized data for KQs qualitatively using summary tables. We integrate syntheses of comparative studies evaluating medical interventions addressed in our 2011 review of therapies for children with ASD[11] if they addressed an agent evaluated in a study identified for the current review.

We attempted to perform a quantitative meta-analysis for the effects of risperidone on outcomes related to challenging behaviors using a multivariate normal response to simultaneously model four outcome scales. However, only three studies satisfied the criteria for inclusion, which included reporting baseline and end-of-treatment (or change from baseline) means and standard deviations. This number of studies prevented us from using a random effects meta-analysis, which was warranted to account for the variation in outcomes. We fit a prototype model using a fixed effects meta-analysis, but the goodness-of-fit evaluation was very poor, so we elected not continue the meta-analysis. We summarize prior meta-analyses and systematic reviews addressing many of the same agents in the Findings in Relation to What is Known section of the report.

Risk of Bias Assessment of Individual Studies

We evaluated the overall methodologic risk of bias of individual studies using the ASD-specific assessment approach we developed and used in our prior reviews of interventions for ASD and informed by the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[12] We developed this tool (Appendix B) because standard risk of bias assessment tools (e.g., Cochrane risk of bias assessment) do not fully account for the complexity of interventions and populations represented in the ASD literature. Specifically, the tool includes questions to address diagnostic approaches and measures of treatment fidelity that may affect outcomes. The tool has not been formally validated.

Two senior investigators assessed each included study independently with disagreements resolved through discussion or by an independent senior investigator/methodologist. Appendix D includes ratings for each study.

Determining Overall Risk of Bias Ratings

We used the thresholds we establish in prior reviews to assess overall high, medium or low risk of bias. We assessed the risk of bias based upon the study-defined primary outcome(s). We assessed each domain described above individually and considered the individual ratings to determine an overall quality assessment of low, moderate, or high risk of bias. We required that studies receive positive scores questions related to randomization and diagnostic approach to be considered low risk of bias. Scores were calculated first by domain and then summed and weighted as described in Table 3 to determine overall study risk. Studies could receive up to two points on the domains of study design, diagnostic approach, participant ascertainment, and intervention, and up to one point on the domains of outcome measurement and statistical analysis.

Table 3. Quality scoring algorithm

Definition and Scoring Algorithm	Rating
Score algorithm for internal validity quality rating	
• ≥8/10 points, including a ++ on study design and ++ on diagnostic approach	Low risk of bias
• ≥6/10 points, including at least a + on intervention	Moderate risk of bias
• ≤5/10 points	High risk of bias

Strength of the Body of Evidence

The assessment of the literature is done by considering both the observed effectiveness of interventions and the confidence that we have in the stability of those effects in the face of future research. The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence, and it can be regarded as insufficient, low, moderate, or high. Strength of evidence describes the adequacy of the current research, both in terms of quantity and quality, as well as the degree to which the entire body of current research provides a consistent and precise estimate of effect. Interventions that have demonstrated benefit in a small number of studies but have not yet been replicated using the most rigorous study designs will therefore have insufficient or low strength of evidence to describe the body of research. Future research may find that the intervention is either effective or ineffective. Strength of the evidence is assessed for a limited set of critical outcomes, typically those related to effectiveness of an intervention.

Methods for applying strength of evidence assessments are established in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[12] and are based on consideration of five domains (Table 4): study limitations, consistency in direction of the effect, directness in measuring intended outcomes, precision of effect, and reporting bias. Strength of evidence is assessed separately for major intervention-outcome pairs and incorporates data from the entire body of reviewed evidence on behavioral interventions (i.e., comparative studies—both RCTs and prospective and retrospective cohort studies—reported in the 2011 review[11] and studies reported in the current review). We required at least one low risk of bias study for moderate strength of evidence and two low risk studies for high strength of evidence. In addition, to be considered "moderate" or higher, intervention-outcome pairs needed a positive response on two out of the three domains other than study limitations.

Once we had established the maximum strength of evidence possible based upon these criteria, we assessed the number of studies and range of study designs for a given intervention-outcome pair, and downgraded the rating when the cumulative evidence was not sufficient to justify the higher rating. The possible grades were:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.

Table 4. Domains used to assess strength of evidence[a]

Domain	Explanation
Study Limitations	Degree to which included studies for a given outcome have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through study design and study conduct.
Consistency	Degree to which included studies find either the same direction or similar magnitude of effect. Assessed through two main elements: • Direction of effect: Effect sizes have the same sign (that is, are on the same side of no effect or a minimally important difference). • Magnitude of effect: The range of effect sizes is similar.
Directness	Extent to which evidence links interventions directly to a health outcome of specific importance for the review, and for comparative studies, whether the comparisons are based on head-to-head studies. Evidence may be indirect in several situations such as:

	• Outcome being graded is considered intermediate in a review that is focused on clinical health outcomes (such as morbidity, mortality). • Data do not come from head-to-head comparisons but rather from two or more bodies of evidence to compare. • Data are available only for proxy respondents instead of directly from patients for situations in which patients are capable of self-reporting and self-report is more reliable.
Precision	Degree of certainty surrounding an effect estimate with respect to a given outcome, based on the sufficiency of sample size and number of events. A body of evidence will generally be imprecise if the optimal information size (OIS) is not met. OIS refers to the minimum number of patients (and events when assessing dichotomous outcomes) needed for an evidence base to be considered adequately powered.
Reporting bias	Degree of selective publishing or reporting of research findings based on the favorability of direction or magnitude of effect.

[a] Excerpted from Berkman et al. 2013[14]

Applicability

We assessed the applicability of findings reported in the included literature addressing our KQs to the general population of children with ASD by determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category. We anticipated that areas in which applicability would be especially important to describe would include ASD severity, comorbidities, age at treatment, and intervention characteristics such provider, dosing/intensity, and setting. Applicability tables for each KQ are in Appendix E.

Peer Review and Public Commentary

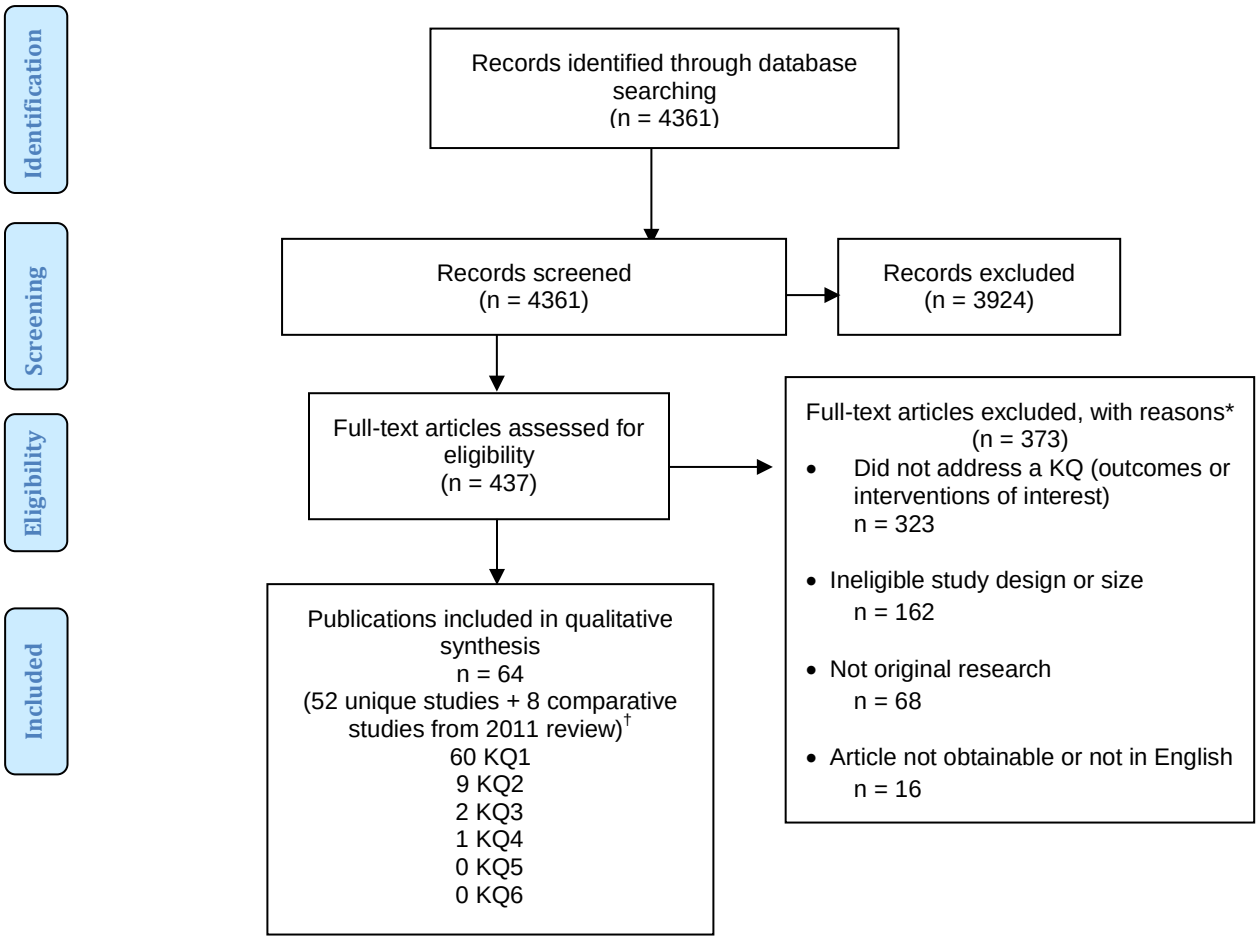
Researchers and clinicians with expertise in treating children with ASD and individuals representing stakeholder and user communities will provide external peer review of this report. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revise the text as appropriate, and document changes and revisions to the report in a disposition of comments report that will be made available 3 months after AHRQ posts the final review on the AHRQ Web site.

Results

Results of Literature Searches for Key Questions

We identified 4361 nonduplicative titles or abstracts with potential relevance, with 437 proceeding to full text review (Figure 2). We excluded 373 studies at full text review. We included 52 unique studies (64 publications) in the review. In addition to these 52 studies published since the completion of our original review of therapies for children with Autism Spectrum Disorder (ASD) in 2011,[11] we include 13 comparative studies addressed in the 2011 review that also addressed an agent used in the current review. Five studies (reported in multiple publications) included in the 2011 review now include followup analyses published since the completion of that report.[15-40] We outline findings from all 60 studies below.

Figure 2. Disposition of studies identified for this review



Numbers next to each Key Question indicate number of unique studies addressing the question. Studies could address more than one Key Question.
*Numbers do not tally as studies could be excluded for multiple reasons.
†We also include analysis of 13 comparative studies reported in our 2011 review of therapies for children with ASD, five of which include new sub-analyses or longer term analyses published since the completion of the 2011 review; thus, we describe a total of 60 studies. Abbreviations: KQ = key question; n = number.

Description of Included Studies

The 60 studies included in the review comprised 57 randomized controlled trials [RCTs] reported in multiple publications,[15-38, 40-100] one nonrandomized trial,[101] and two retrospective cohort studies.[102, 103] We considered 33 studies to have low risk of bias,[15-38, 40, 41, 44-47, 51-53, 55-58, 63-66, 71, 73, 74, 80-87, 91-96] 22 to have moderate,[42, 43, 49, 50, 54, 59-62, 67-70, 72, 75, 77-79, 88-90, 97, 99, 100, 102] and five to have high risk.[48, 76, 98, 101, 103] Despite the high number of low and moderate risk of bias studies, few studies addressed the same interventions or outcomes, and most studies included few participants, evaluated only in the short term (< 6 months); thus, evidence for many agents remains insufficient. Table 5 outlines key study characteristics. Because few studies addressed sub-questions under Key Questions (KQ) 1 and 2, we present results in the aggregate under each of these KQ.

Table 5. Overview of studies

Characteristic	RCTs (n=57)	Nonrandomized trials (n=1)	Retrospective Cohort Studies (n=2)	Total Literature
Intervention category				
Antipsychotics	8	0	1	9
Stimulants	3	0	0	3
Norepinephrine reuptake inhibitors	2	0	0	2
Nutrition and diet	14	0	0	14
Risperidone adjuncts	12	0	0	12
Hyperbaric oxygen therapy	3	0	0	3
Other medical approaches*	14	1	1	16
Treatment duration				
<1-4 weeks	7	1	0	8
5-8 weeks	12	0	0	12
9-12 weeks	24	0	0	24
13-20 weeks	5	0	0	5
21-36 weeks	7	0	1	8
>52 weeks	2	0	1	3
Region of Study Conduct				
Africa	2	0	0	2
Asia	19	1	0	20
Australia	2	0	0	2
Europe	7	0	0	7
North America	27	0	2	29
Risk of Bias				
Low	33	0	0	33
Moderate	21	0	1	22
High	3	1	1	5
Total N participants	**3090**	**36**	**186**	**3312**

*Includes two of melatonin, two of bumetanide, two of donepezil, and one each of neurostimulation, amantadine, divalproex, stem cell transplantation, oxytocin, mecamylamine, N-acetylcysteine, prednisolone, tetrahydrobiopterin, and citalopram. N = Number; RCT = Randomized Controlled Trial

Gray Literature

Our searches of ClinicalTrials.gov and other trial registers did not yield additional eligible studies for the review. We did not receive information in response to requests for scientific information from manufacturers or device makers. We used information from organization web sites searched to provide additional context for the discussion section of the report.

KQ1. Benefits and Harms of Medical Treatments

Studies of Antipsychotics

Key Points

- Four RCTs addressing risperidone reported significant improvements in measures of irritability and other challenging behaviors in the treatment group compared with placebo in the short-term (≤6 months), with continued positive effects over a mean 21-month treatment period in an uncontrolled extension study. Side effects including somnolence and weight gain were significant.
- One RCT comparing risperidone plus parent training reported significant improvements in irritability, hyperactivity, and repetitive behavior in children receiving combined therapy compared with risperidone alone.
- Two RCTs of aripiprazole reported statistically significant improvements in irritability and challenging behavior in the treatment groups compared with placebo over 8 weeks of treatment and maintenance of improvements in a 52-week uncontrolled extension. Harms were also significant. Another RCT reported no differences in time to relapse (return of significant negative symptoms) between children taking aripiprazole versus placebo; quality of life measures also did not differ between groups.
- Two small studies comparing risperidone with aripiprazole reported no significant differences in effects on challenging behaviors or general improvement; one study noted no significant differences in weight gain associated with each agent.
- Strength of the evidence was high for short-term improvements in challenging behaviors associated with risperidone and aripiprazole and high for significant harms associated with these agents; low for longer term (> 6 months) behavioral improvements associated with aripiprazole; and low for longer term improvements with risperidone as two studies of at least 6 months duration assessed this agent (including one open label extension with no control arm). As only one small RCT compared aripiprazole and risperidone and reported usable data, strength of the evidence was insufficient to assess effects on any outcome. Other outcomes (e.g., ASD symptom severity, repetitive behavior, adaptive behavior) were addressed in single studies; thus we considered strength of evidence insufficient for all other intervention/outcome pairs.

Overview of the Literature

We identified eight unique RCTs (reported in multiple publications and including comparative studies identified for the current review and those reported in our 2011 review[11]) addressing antipsychotics[15-21, 28-41, 46, 60, 67, 68, 71, 73, 74] and one retrospective cohort that reported harms data only.[102] Six studies had low risk of bias,[15-21, 28-40, 46, 67, 68, 71, 73, 74] and three had

moderate risk.[60, 67, 68, 102] Studies included a total of 1053 children ranging in age from 2 to 20 years and were conducted in the United States (n=6), Canada (n=1), Iran (n=1), and India (n=1).

Two RCTs addressed aripiprazole compared with placebo;[15-21, 46] four addressed risperidone compared with placebo;[28-38, 40, 41, 60, 67, 68, 73, 74] one addressed risperidone compared with placebo plus parent training;[38-40] and one compared risperidone and aripiprazole.[71] A retrospective cohort compared these agents and reported differences in weight gain.[102]

Five of these eight RCTs were also included in our 2011 review,[15-21, 28-41, 60, 67, 68, 74, 104] and investigators of four of these studies have published additional analyses of participants included in the original trials. These studies included two "families" of papers that report post-hoc and additional or combined analyses of participants in the initial trials. The first family of studies, conducted by Research Units on Pediatric Psychopharmacology (RUPP) Autism Network investigators, assessed risperidone and included an initial 8-week trial comparing risperidone and placebo in 101 children;[34] one paper reporting potential moderators of effect in the 8-week trial;[29]one paper reporting parent concerns assessed during the initial 8-week trial;[35] one paper reporting social interaction measures in these participants;[40] one reporting measures of repetitive behavior;[38] and one paper that reported cognitive changes in a subset of children in the original 8-week trial.[30] This family also includes another paper that assessed longer term (16 weeks) effects in children who responded to risperidone in the original 8-week trial plus children who originally received placebo and were considered placebo nonresponders but had subsequent positive response to risperidone (total n=63);[36] 32 of these children went on to enroll in an RCT comparing either continued risperidone or risperidone with gradual placebo replacement.[31] The investigators followed up these reports with a paper reporting additional social interaction and stereotypy analyses of the 101 original participants in the 8-week trial and the 63 participants in the extension trial,[32] analyses of weight changes in the 63 children in the extension trial,[33] and analysis of adaptive behavior measures in 48 of these 63 children for whom such data were available.[37] Finally, the family includes a paper reporting longer term effects (mean 21 months) in 84 of the original 101 trial participants (38 of whom participated in the extension trial); among these 84 individuals, 53 continued to receive risperidone in the month before followup.[28] Another paper reports changes in prolactin levels in these children after 8 weeks, 6 months, and roughly 22 months of risperidone treatment.[41]

The second family of papers assessed aripiprazole and includes one 8-week trial comparing fixed doses of aripiprazole with placebo;[20] another 8-week trial comparing titrated doses of aripiprazole with placebo;[21] one paper reporting safety data in these two original trials;[19] another reporting health-related quality of life measures assessed in the two original trials;[17] and another outlining Aberrant Behavior Checklist (ABC) data in the two trials.[16] The family also includes as open label extension that combined children from the original RCTs (both treatment and placebo groups) and added children who had not participated in the prior studies (de novo subjects) and in which all 330 participants received 52 weeks of aripiprazole.[15] Finally, this family includes a paper reporting adverse events/safety data for children in the 52-week open label extension.[18]

Studies addressing antipsychotics also included a related group of studies: one RCT conducted by RUPP investigators compared risperidone with risperidone plus parent training in 124 children.[39] Two subsequent papers reported data on social interaction and repetitive behavior measures from both this RCT and the 8-week RUPP trial of risperidone compared with placebo but did not combine participants in either study in their analyses.[38, 40] Across studies, treatment duration ranged from 8 weeks to over 2 years, with followup immediately post-treatment in all studies. Four studies were funded by drug manufacturers.[20, 21, 46, 67, 68, 73, 74]

Detailed Analysis

The literature on antipsychotic effects in children with ASD reports a variety of outcomes but converges on the ABC, a rating scale completed by caregivers of individuals with ASD. Studies also typically assessed potential side effects or harms, including assessment of weight gain, somnolence, and gastrointestinal symptoms and used the Clinical Global Impression (CGI) rating scale. Studies of antipsychotics addressed either risperidone or aripiprazole and reported significant improvements in measures of challenging behavior in the short term (<6 months) in children receiving the medications compared with those receiving placebo. Harms of these agents, including extrapyramidal symptoms and weight gain, were also significant. Studies reporting longer term followup (up to 21 months for risperidone) reported continued effectiveness in most children but did not include control groups. We report brief summaries of outcomes reported in each study below and end of treatment outcomes on the ABC and CGI in Tables 6-9. Appendix F includes detailed summary tables outlining other outcomes.

Studies of Risperidone

The four RCTs comparing risperidone and placebo included one study (reported in multiple publications) conducted by RUPP investigators (low risk of bias).[28-38, 40, 67, 68] In the initial 8-week trial including 101 children,[34] baseline ratings of irritability were similar across risperidone and placebo arms. The risperidone arm had significantly greater decreases (improvement) in ABC-Irritability scores compared with the placebo arm (improvements of 15.1 vs. 3.6 points, p<0.001). Clinician ratings of outcomes considered by parents to be chief concerns paralleled these findings of significant improvement in challenging behavior in the risperidone group.[35] In other sub-analyses of participants in the original 8-week trial, ABC-Social Withdrawal scores were significantly improved in the treatment group compared with placebo (mean difference of 3.82, p=0.05, effect size: 0.42) as were scores on the Children's Yale-Brown Obsessive Compulsive Scale-ASD (CYBOCS-ASD) (p=0.005, effect size: 0.74), but scores on cognitive measures in a subset of 38 participants who were able to complete the assessments typically did not differ between groups, though no decline in cognitive skills was associated with treatment.[30, 38, 40]

In another series of followup papers from this original RCT, investigators randomized responders to risperidone from the original trial and children who originally received placebo and were considered placebo nonresponders but had subsequent positive response to risperidone to either risperidone or risperidone with gradual placebo replacement for 16 weeks.[31, 36] More children in the gradual replacement arm (n=10, 62.5%) compared with risperidone (n=2, 12.5%, p=0.01) experienced relapse (25% increase in ABC-Irritability score and CGI-Improvement rating of much or very much worse compared with baseline). In followup analyses of these participants plus children from the initial 101 in the 8-week trial, children receiving risperidone for up to 16 weeks had significant improvements in parent-rated measures of affect, repetitive and restricted behaviors, and sensory responses compared with children receiving placebo, but measures of social relatedness or language did not differ between groups.[32] In a report of 48 children participating in the 16-week extension and receiving risperidone, scores on Vineland Adaptive Behavior Scales (VABS) measures of communication and daily living skills improved significantly over the treatment period; however, this analysis lacked a control arm.[37]

In an extension of these analyses, investigators followed 84 of the initial 101 children in the 8-week trial (38 also participated in the extension trials).[28] These 84 children received risperidone for some portion of the mean 21-month uncontrolled followup; children could have

received another antipsychotic or other medication, but 96 percent received risperidone over the followup period, and 68 percent were taking an antipsychotic in the month prior to followup. CGI-Severity scores improved significantly from baseline, regardless of treatment in the original trial (effect size: -0.75) with risperidone. ABC-Irritability similarly improved significantly from baseline (effect size -1.01) as did the ABC-Social Withdrawal (effect size: -0.85), ABC-Stereotypy (effect size: -0.82), ABC-Hyperactivity (effect size: -1.07), and ABC-Inappropriate Speech (-0.41) scales. Scores on the CYBOCS also improved significantly from baseline (effect size: -0.79), while scores on the VABS typically improved, but not significantly. IQ did not change significantly with risperidone.

In another RCT (low risk of bias) comparing a low dose risperidone group, a high dose risperidone group, and a placebo group (total n=96) funded by the manufacturer of risperidone, baseline scores for ABC-Irritability and the CGI scales were similar across all groups.[73, 74] The high dose risperidone arm had the greatest improvement in ABC-Irritability scores, followed by the low-dose group and placebo. The difference between high dose risperidone and placebo alone was statistically significant ($p<0.001$), but differences between low dose and placebo were not. The study reported similar improvements in CGI, with the greatest decrease in CGI scores for high dose risperidone and statistically significant differences between only the high dose group and placebo ($p<0.001$). In a 6-month open label extension of risperidone including 79 (56 completers) of the 96 children originally enrolled in the RCT, children received either fixed dose or flexibly dose risperidone with a median dose of 0.875mg/day in the open-label phase. All groups improved from baseline on the ABC-Irritability scale, with no significant differences between groups. Other measures taken at the end of the study included ABC-Hyperactivity, ABC-Stereotypic Behavior, ABC-Inappropriate Speech, ABC-Social Withdrawal, CYBOCS, CGI-Severity and CGI-Improvement, all of which showed improvement from baseline with no significant group differences.

One moderate risk of bias RCTs reported in the 2011 review reported statistically significant improvements on the ABC-Irritability, Stereotypy, and Hyperactivity subscales compared with the placebo group.[67, 68] The final RCT (moderate risk of bias) assessed outcomes after 6 months of risperidone treatment using a variety of general rating scales but provided quantitative data on only some of these scales.[60] The primary outcome measures were parent ratings on the Childhood Autism Rating Scale (CARS) and clinician ratings on the Children's Global Assessment Scale (CGAS). The study only reported CARS median ratings for those participants with at least a 20 percent response; more children receiving risperidone achieved this goal compared with placebo (12 vs. 0, $p<0.001$). Average ratings on the CGAS were similar in the risperidone (29.8) and placebo (32.7) arms, with more improvement in the risperidone vs. placebo arms ($p=0.04$). Parent-rated scores did not differ between groups.

Table 6. Key outcomes in studies comparing risperidone and placebo

Author, Year, Study Design Groups (Dose), N Enrollment / N Final Treatment Duration/Follow-Up Time Point Post-Treatment Risk Of Bias	Baseline Scores, Mean ±SD	Post-Treatment Scores, Mean ± SD

Scahill 2015[34] RCT G1: Risperidone (up to 2.5 mg/kg), 49/49 G2: Placebo (NA), 52/52 8 weeks/EOT Moderate RoB	ABC-Irritability G1: 26.2 ± 7.9 G2: 25.5 ± 6.6 ABC-Lethargy/Social Withdrawal G1: 16.4 ± 8.2 G2: 16.1 ± 8.7 ABC-Stereotypic Behavior G1: 10.6 ± 4.9 G2: 9 ± 4.4 ABC-Hyperactivity G1: 31.8 ± 9.6 G2: 32.3 ± 8.5 ABC-Inappropriate Speech G1: 4.8 ± 4.1 G2: 6.5 ± 3.6 CGI-S – Moderate G1: 9 (18) G2: 9 (18) CGI-S – Marked G1: 27 (55) G2: 28 (57) CGI-S – Severe G1: 12 (24) G2: 12 (24) CGI-S – Extreme G1: 1 (2) G2: 0 (0)	ABC-Irritability G1: 11.3 ± 7.4 G2: 21.9 ± 9.5 G1 vs G2: p<0.001; ES=1.2 ABC-Lethargy/Social Withdrawal G1: 8.9 ± 6.4 G2: 12 ± 8.3 G1 vs G2: p=0.03, ES=0.4 ABC-Stereotypic Behavior G1: 5.8 ± 4.6 G2: 7.3 ± 4.8 G1 vs G2: p<0.001 ES=0.8 ABC-Hyperactivity G1: 17 ± 9.7 G2: 27.6 ± 10.6 G1 vs G2: p<0.001 ABC-Inappropriate Speech G1: 3 ± 3.1 G2: 5.9 ± 3.8 G1 vs G2: p=0.03. ES=0.3 CGI-I – Much Improved or very much improved + 25% reduction on ABI-I G1: 34 (69) G2: 6 (12)
Scahill 2015[36] RCT G1: Risperidone (2.5 mg/day), 63/63 G2: Placebo-Substitution (NA), NA 4 weeks during open label extension/EOT Moderate RoB	**End of initial 8 wks of treatment exposure** CGI-I – Very much improved G1: 19 (30.2) G2: ND CGI-I – Much Improved G1: 42 (66.7) G2: ND CGI-I Minimally Improved G1: 0 (0) G2: ND CGI-I – No Change G1: 2 (3.2) G2: ND CGI-I – Worse G1: 0 (0) G2: ND CGI-I – Much Worse G1: 0 (0) G2: ND	ABC-Irritability G1: 11.7 ± 8 G2: ND ABC-Social Withdrawal/Lethargy G1: 6.8 ± 5.9 G2: ND ABC-Stereotypy G1: 5.8 ± 4.7 G2: ND ABC-Hyperactivity G1: 15.8 ± 10.2 G2: ND ABC-Inappropriate Speech G1: 3.4 ± 3.2 G2: ND

	ABC-Irritability G1: 9.5 ± 6.8 G2: ND ABC-Social Withdrawal/Lethargy G1: 7.3 ± 5.4 G2: ND ABC-Stereotypy G1: 4.9 ± 4.3 G2: ND ABC-Hyperactivity G1: 15.1 ± 10 G2: ND ABC-Inappropriate Speech G1: 3.4 ± 3.6 G2: ND	
Scahill 2015[28] RCT G1: Risperidone (2.5 mg/day), 57/55 G2: Placebo (NA), 27/26 Mean 21 months/2 Years post-treatment Moderate RoB	ABC-Irritability G1: 27.22 ± 7.28 G2: 23.44 ± 7.24 ABC-Social Withdrawal G1: 16.05 ± 8.55 G2: 18.52 ± 9.72 ABC-Stereotypic Behavior G1: 10.5 ± 4.43 G2: 8.84 ± 5.22 ABC-Hyperactivity/Noncompliance G1: 34.3 ± 7.95 G2: 28.58 ± 10.4 ABC-Inappropriate Speech G1: 5.71 ± 3.93 G2: 5.59 ± 4.03 CGI-Severity G1: 5.09 0.7 G2: 5.23 0.65	**2 yrs post-treatment** ABC-Irritability G1: 14.82 ± 8.4 G2: 17.78 ± 10.82 G1 vs G2: p=0.0147 ABC-Social Withdrawal G1: 8.43 ± 6.77 G2: 13.33 ± 8.73 G1 vs G2: p=0.0130 ABC-Stereotypic Behavior G1: 6.02 ± 4.4 G2: 6.76 ± 5.37 G1 vs G2: p=0.0866 ABC-Hyperactivity/Noncompliance G1: 17.68 ± 10.16 G2: 23.38 ± 12.06 G1 vs G2: p=0.0020 ABC-Inappropriate Speech G1: 3.86 ± 3.01 G2: 5.15 ± 4.24 G1 vs G2: p=0.0433 CGI-Severity G1: 4.4 ± 0.89 G2: 4.65 ± 1.09 G1 vs G2: p=0.3004
Kent 2013[73, 74] RCT G1: Risperidone (0.125-0.175 mg/day; low dose), 30/25 G2: Risperidone (1.25-1.75 mg/day; high dose), 31/25 G3: Placebo (NA), 35/27 6 weeks/EOT Low RoB	ABC-Irritability G1: 27.1 ± 6.26 G2: 28.0 ± 7.81 G3: 28.9 ± 6.10 CGI – Severity G1: 5.1 ± 0.92 G2: 5.0 ± 0.78 G3: 4.9 ± 0.67	Mean change in: ABC-Irritability G1: -7.4 ± 8.12 G2: -12.4 ± 6.52 G3: -3.5 ± 10.67 G1 vs G3: p=ns G2 vs G3: p<0.001 CGI – Severity G1: -0.4 ± 0.73 G2: -1.0 ± 0.78 G3: -0.3 ± 0.79 G1 vs G3: p=ns

		G2 vs G3: p<0.001
Kent 2013[73, 74] RCT G1: Risperidone (0.125-0.175 mg/day; low dose)/Risperidone, 30/25 G2: Risperidone (1.25-1.75 mg/day; high dose)/Risperidone, 31/25 G3: Placebo/Risperidone (NA), 35/27 6 weeks/End of open label trial Low RoB	ABC-Irritability G1: 13.4 ± 3.99 G2: 14.4 ± 4.64 G3: 13.7 ± 2.66 ABC-Hyperactivity G1: 30.1 ± 11.46 G2: 33.8 ± 9.75 G3: 31.4 ± 8.60 ABC-Stereotypic Behavior G1: 9.3 ± 5.17 G2: 11.5 ± 5.06 G3: 10.5 ± 5.26 ABC-Inappropriate Speech G1: 6.6 ± 3.49 G2: 7.5 ± 2.78 G3: 5.9 ± 3.42 ABC-Social Withdrawal G1: 18.2 ± 9.71 G2: 21.4 ± 9.09 G3: 18.1 ± 10.16 CGI-Severity G1: 5.1 ± 0.93 G2: 5 ± 0.75 G3: 4.9 ± 0.67	**Mean change score** ABC-Irritability G1: -13.2 ± 9.29 G2: -13 ± 10.55 G3: -11.8 ± 7.68 ABC-Hyperactivity G1: -10.5 ± 12.42 G2: -12.3 ± 11.78 G3: -11.7 ± 8.54 ABC-Stereotypic Behavior G1: -4.2 ± 6.51 G2: -4.6 ± 5.14 G3: -2.8 ± 4.12 ABC-Inappropriate Speech G1: -1.8 ± 3.93 G2: -2.1 ± 3.07 G3: -1.5 ± 2.69 ABC-Social Withdrawal G1: -8.3 ± 9.03 G2: -10.4 ± 8.57 G3: -6.9 ± 8.08 CGI-Severity G1: -1 ± 1.02 G2: -1.3 ± 1.17 G3:-0.9 ± 0.88 CGI-Much or Very Much Improved G1: 14 (58) G2: 15 (60) G3: 20 (69) G1 vs. G2 vs. G3: p=ns
Shea 2004[67, 68] RCT G1: Risperidone (0.02 mg/kg/day), 39/39 G2: Placebo (NA), 38/38 8 weeks/EOT Moderate RoB	ABC-Irritability G1: 18.9 ± 8.8 G2: 21.2 ± 9.7 ABC-Hyperactivity G1: 13.7 ± 7 G2: 14.3 ± 8.2 ABC-Social Withdrawal/Lethargy G1: 27.3 ± 9.7 G2: 30.9 ± 8.8 ABC-Stereotypy G1: 4.6 ± 3.4 G2: 4.8 ± 3.7 ABC-Inappropriate Speech G1: 7.9 ± 5 G2: 8.1 ± 5.6	Mean Change Scores ABC-Irritability G1: -12.1 ± 5.8 G2: -6.5 ± 8.4 G1 vs G2: p≤0.001 ABC-Hyperactivity G1: -8.6 ± 5.9 G2: -5.7 ± 6.9 G1 vs G2: p≤0.01 ABC-Social Withdrawal/Lethargy G1: -14.9 ± 6.7 G2: -7.4 ± 9.7 G1 vs G2: p≤0.001 ABC-Stereotypy G1: -2.6 ± 2.6 G2: -1.6 ± 3 G1 vs G2: p≤0.05 ABC-Inappropriate Speech G1: -4.3 ± 3.8

		G2: -2.4 ± 4 G1 vs G2: p≤0.05

ABC = Aberrant Behavior Checklist; CGI-I - Clinical Global Impression Scale Improvement, EOT = End Of Treatment; ES = Effect Size; G = Group; kg = Kilograms; mg = Milligrams; mL = milliliters; NA = Not Applicable; ND = No Data; RCT = Randomized Controlled Trial; RoB = Risk of Bias; SD = Standard Deviation

Studies Comparing Risperidone Plus Parent Training

A final RCT (low risk of bias) compared risperidone with risperidone plus parent training in children with Pervasive Development Disorder and severe behavior problems.[38-40] The original RCT was included in our 2011 review.[11] In the initial RCT, children with ASD and significant tantrums, self-injury, and aggression received either combined treatment of risperidone plus am manualized parent training program or risperidone alone.[39] After 24 weeks of treatment, Home Situations Questionnaire scores declined (i.e., improved) for 71 percent of the combined group and 60 percent of the medication only group (p=0.006, effect size=0.34). In addition, the ABC-Irritability, stereotypic behaviors, and hyperactivity/noncompliance subscales all showed significant group differences over time, with children of parents who received the parent training having less severe symptoms in each of the domains. One post-hoc analysis[40] of children reported effect sizes on the ABC-Social withdrawal subscale of 0.65 in the risperidone only group and 0.65 in the combination group; scores were significantly better than those of the placebo arm in the original 8-week trial or risperidone vs. placebo.[34] In another subanalysis,[38] effect sizes on the CYBOCS-ASD were 0.88 in the risperidone only group and 0.86 in the combination group, both significantly improved compared with the placebo arm in the original RUPP risperidone trial.[34]

Table 7. Key outcomes in studies comparing risperidone and parent training

Author, Year, Study Design Groups (Dose), N Enrollment / N Final Treatment Duration/Follow-Up Time Point Post-Treatment Risk Of Bias	Baseline Scores, Mean ±SD	Post-Treatment Scores, Mean ± SD
Scahill 2015[38-40] RCT G1: Risperidone (3.5 mg/day), 49/47 G2: Risperidone + Parent Training (up to 3.5 mg/day + mean of 10.9 sessions), 75/70 24 weeks/EOT Moderate RoB	CGI-S – Moderate G1: 14 (28.6) G2: 25 (33.3) CGI-S – Marked G1: 19 (38.8) G2: 33 (44) CGI-S – Severe G1: 15 (30.6) G2: 17 (22.7) CGI-S – Extreme G1: 1 (2) G2: 0 (0) ABC – Irritability G1: 29.7 ± 6.1 G2: 29.3 ± 6.97 ABC – Social Withdrawal G1: 17.1 ± 8.37	ABC – Irritability G1: 14.53 ± 9.9 G2: 10.96 ± 6.64 ABC – Social Withdrawal G1: 6.44 ± 7.16 G2: 4.26 ± 5.17 ABC – Stereotypic Behavior G1: 6.25 ± 5.68 G2: 3.2 ± 4.09 ABC – Hyperactivity/Noncompliance G1: 20.78 ± 12.38 G2: 15.38 ± 10.23 ABC – Inappropriate Speech G1: 3.3 ± 3.66 G2: 2.56 ± 2.93

	G2: 15.2 ± 9.01 ABC – Stereotypic Behavior G1: 10.6 ± 5.46 G2: 7.59 ± 5.2 ABC – Hyperactivity/Noncompliance G1: 36.1 ± 6.86 G2: 35.3 ± 9.3 ABC – Inappropriate Speech G1: 6.37 ± 4.03 G2: 5.75 ± 3.43	

ABC = Aberrant Behavior Checklist; CGI-S - Clinical Global Impression Scale - Severity, EOT = End Of Treatment; G = Group; mg = Milligrams; RCT = Randomized Controlled Trial; RoB = Risk of Bias; SD = Standard Deviation

Studies of Aripiprazole

Two 8-week RCTs (low risk of bias) of aripiprazole compared with placebo were reported in our 2011 review.[20, 21] In these two studies, baseline ratings of irritability were similar across aripiprazole and placebo arms. Decreases in ABC-Irritability were significantly greater for the aripiprazole arms in both studies, with improvements of 12.4-14.4, in comparison to the placebo arms, with improvements of 5.0-8.4. The trial with differing set doses of aripiprazole demonstrated increasing response with increasing dose.[20] Overall, the results of the trial that used titration following clinical judgment were more pronounced.[21] Decreases (improvements) in ABC-Hyperactivity and Stereotypy subscales were significantly greater in children receiving aripiprazole compared with placebo arms. Scores in the ABC-Inappropriate Speech subscale were also significantly improved in the treatment group vs. placebo in the flexibly dosed study but not in the fixed dose RCT. Both studies also used the CYBOCS-Pervasive Development Disorder (CY-BOCS-PDD) scale to assess repetitive behavior, finding no baseline differences between the groups but a greater decrease in the aripiprazole compared with placebo arms (2.4-3.8 vs. 0.8-1.7). A number of other outcomes were measured in these two studies, but none outside of challenging behavior and repetitive behavior yielded statistically significant findings once corrected for multiple comparisons.

Post-hoc analyses of these RCTs analyzed changes in ABC scores[16] and quality of life measures.[17] The first post-hoc analysis[16] analyzed the following changes in ABC subscales. Scores on the ABC-Irritability, Stereotypy, Hyperactivity, and Inappropriate Speech subscales were significantly improved in the aripiprazole arms compared with placebo (all p values <0.05), typically with greater decreases in the flexibly dosed group compared with the fixed dose group. Scores on the Social Withdrawal subscale did not differ significantly between treatment and placebo groups. Compared with placebo, the pooled aripiprazole groups had greater improvements in total health-related quality of life scores and emotional, social, and cognitive functioning scores measured using the Pediatric Quality of Life Inventory (all p values < 0.05).[17] Children who received aripiprazole were also more likely to have clinically meaningful improvement on all these scales compared with those receiving placebo (odds ratios ranging from 1.2 to 2.2, p values <0.05).

Investigators extended these 8-week studies with an uncontrolled, 52-week open label analysis including 70 children who had received placebo in the original RCTs, 174 who had received aripiprazole, and 86 “de novo” subjects.[15] Primary outcomes included the ABC-Irritability and CGI-Severity scales. ABC-Irritability mean scores at baseline were higher for the

de novo (23.2±8.9) and prior placebo (21.5±9.8) groups compared with the prior aripiprazole group (15.0±9.2). Mean change from baseline in the de novo group was -8.0 ± -10.1 and in the prior placebo group was -6.1 ± 11.9. Improvements in scores in the de novo and prior aripiprazole groups occurred in first 8 weeks of the open label phase. The CGI decreased in the same manner, with greater reductions (improvements) in the de novo and prior placebo groups than in the prior aripiprazole group, in which improvements reported in the prior RCTs were maintained. Scores in the ABC-Hyperactivity subscale and CYBOCS followed similar patterns.

An additional low risk of bias RCT randomized 85 children who had shown a stable improvement (≥ 25% decrease in ABC-Irritability scores for 12 weeks) in an initial 13-26 week open label phase to continued, flexibly dosed aripiprazole or placebo until relapse (defined as ≥25% increase in ABC-Irritability score, CGI ratings of worse or much worse, loss-to-followup plus elevated scores, elevated scores plus initiation of other medication to treat symptoms, or discontinuation due to worsening symptoms) or 16 weeks.[46] The difference between the two groups in time to relapse was not statistically significant (35% in the aripiprazole arm at 16 weeks vs. 52% in placebo, hazard ratio=0.57, 95% CI: 0.28 to 1.12, NNT=6). Mean change in the ABC-Irritability and Social Withdrawal scores or CGI-Improvement score from baseline to week 16 did not differ between groups (p≥0.05), but children in the placebo group had greater increases (i.e., worsening behavior) on the ABC-Hyperactivity and Inappropriate Speech subscales than did children in the treatment group (p values <0.05); pediatric quality of life measures also did not differ between groups.

Table 8. Key outcomes in studies comparing aripiprazole and placebo

Author, Year, Study Design Groups (Dose), N Enrollment / N Final **Treatment Duration/Follow-Up Time Point Post-Treatment** **Risk Of Bias**	**Baseline Scores, Mean ±SD**	**Post-Treatment Scores, Mean ± SD**
Marcus 2011[20] RCT G1: Aripiprazole (5 mg/kg), 53/44 G2: Aripiprazole (10 mg/kg), 59/49 G3: Aripiprazole (15 mg/kg), 54/47 G4: Placebo (NA), 52/38 8 weeks/EOT Moderate RoB	ABC-Irritability G1: 28.6 ± 7.6 G2: 28.2 ± 7.4 G3: 28.9 ± 6.4 G4: 28 ± 6.9 ABC-Hyperactivity/Noncompliance G1: 33.1 ± 1.4 G2: 33.7 ± 1.3 G3: 32.2 ± 1.4 G4: 31 ± 1.4 ABC-Stereotypic Behavior G1: 11.4 ± 0.8 G2: 11.6 ± 0.8 G3: 11.6 ± 0.8 G4:10.7 ± 0.8 ABC-Social Withdrawal/Lethargy G1: 17.7 ± 1.4 G2: 16.8 ± 1.3 G3: 18.9 ± 1.4 G4: 18 ± 1.5 ABC-Inappropriate Speech	**Change scores** ABC-Irritability G1: -12.4 G2: -13.2 G3: -14.4 G4: -8.4 G1 v G4: p=0.032 G2 v G4: p=0.008 G3 v G4: p=0.001 ABC-Hyperactivity/Noncompliance G1: -14 ± 1.6 G2: -13.3 ± 1.5 G3: -16.3 ± 1.6 G4: -7.7 ± 1.7 G1 v G4: p≤0.005 G2 v G4: p≤0.05 G3 v G4: p≤0.001 ABC-Stereotypic Behavior G1: -4.5 ± 0.68 G2: -4.2 ± 0.63 G3: -4.5 ± 0.66 G4:-1.8 ± 0.69

	G1: 5.8 ± 0.6 G2: 6.8 ± 0.5 G3: 6.3 ± 0.5 G4: 5.9 ± 0.6 CGI-S G1: 5 ± 0.1 G2: 4.9 ± 0.1 G3: 5.1 ± 0.1 G4: 4.7 ± 0.1	G1 v G4: p≤0.005 G2 v G4: p≤0.05 G3 v G4: p≤0.005 ABC-Social Withdrawal/Lethargy G1: -5.8 ± 1.2 G2: -4.9 ± 1.1 G3: -7.9 ± 1.1 G4: -5.2 ± 1.2 ABC-Inappropriate Speech G1: -2 ± 0.5 G2: -1.8 ± 0.4 G3: -2.3 ± 0.4 G4: -1.1 ± 0.5 CGI-S G1: -0.9 ± 0.2 G2: -1 ± 0.1 G3: -1.1 ± 0.2 G4: -0.6 ± 0.2
Marcus 2011[21] RCT G1: Aripiprazole (2-15 mg/kg), 47/39 G2: Placebo (NA), 51/36 8 weeks/EOT Moderate RoB	ABC-Irritability G1: 29.6 ± 6.4 G2: 30.2 ± 6.5 ABC-Hyperactivity/Noncompliance G1: 34.1 G2: 34.7 ABC-Stereotypic Behavior G1: 11.9 G2: 10.7 ABC-Inappropriate Speech G1: 7 G2: 7	**Change Scores** ABC-Irritability G1: -12.9 G2: -5 G1 vs G2: p<0.001 ABC-Hyperactivity/Noncompliance G1: -12.7 G2: -2.8 G1 vs G2: p<0.001 ABC-Stereotypic Behavior G1: -4.8 G2: -2 G1 vs G2: p<0.001 ABC-Inappropriate Speech G1: -2.5 G2: -0.4 G1 vs G2: p<0.001 CGI-Severity G1: -1.2 G2: -0.4 CGI-I – Very much improved or much improved G1: 31 (67) G2: 8 (16) CGI-I – Minimally improved G1: 7 (15) G2: 10 (20) CGI-I – No change G1: 6 (13) G2: 22 (45) CGI-I – Minimally worse G1: 2 (4)

		G2: 5 (10) CGI-I – Much or very much worse G1: 0 (0) G2: 4 (8)
Marcus 2011[15] RCT G1: De Novo Subjects (2-15 mg/kg), 84/55 G2: Prior Placebo (2-15 mg/kg), 69/37 G3: Prior Aripiprazole (2-15 mg/kg), 169/107 52 weeks Moderate RoB	CGI-Severity G1: 4.8 ± 1 G2: 4.2 ± 1 G3: 3.9 ± 1.1 ABC-Irritability G1: 23.2 ± 8.9 G2: 21.5 ± 9.8 G3: 15 ± 9.2 ABC-Lethargy/Social Withdrawal G1: 14.6 ± 8.6 G2: 11.3 ± 9.2 G3: 10.4 ± 8.9 ABC-Stereotypic Behavior G1: 8.1 ± 5.2 G2: 9.1 ± 5.6 G3: 6.4 ± 5.5 ABC-Hyperactivity G1: 28.4 ± 10.9 G2: 25.8 ± 13.2 G3: 18.4 ± 12 ABC-Inappropriate Speech G1: 5.8 ± 3.2 G2: 5.7 ± 4.2 G3: 4.2 ± 3.6	CGI-Severity G1: -1 ± 0.8 G2: -0.6 ± 1.2 G3: -0.1 ± 1 ABC-Irritability G1: -8 ± 10.1 G2: -6.1 ± 1.9 G3: 0.7 ± 10.2 ABC-Lethargy/Social Withdrawal G1: -6.4 ± 7.9 G2: -4.1 ± 7.2 G3: -2.3 ± 6.4 ABC-Stereotypic Behavior G1: -2.7 ± 3.1 G2: -1.9 ± 4.1 G3: -0.5 ± 4.4 ABC-Hyperactivity G1: -12.3 ± 8.5 G2: -9.1 ± 11.5 G3: 0.6 ± 10.3 ABC-Inappropriate Speech G1: -2 ± 2.5 G2: -1.8 ± 3 G3: -0.3 ± 2.4
Marcus 2011[16] RCT G1: Aripiprazole (2-15 mg/kg; flexibly dosed study), 46/46 G2: Aripiprazole (5 mg/kg), 52/52 G3: Aripiprazole (10 mg/kg), 59/59 G4: Aripiprazole (15 mg/kg), 53/53 G5: Placebo (flexibly dosed study) 49/49 G6: Placebo (fixed-dose study) 49/49 8 weeks/EOT Moderate RoB	ABC-Irritability G1: 29.6 ± 1 G2: 28.3 ± 1 G3: 27.6 ± 0.9 G4: 28.3 ± 1 G5: 30.8 ± 1 G6: 26.9 ± 1 ABC-Social Withdrawal/Lethargy G1: 19.9 ± 1.6 G2: 17.7 ± 1.4 G3: 16.8 ± 1.3 G4: 18.9 ± 1.4 G5: 18.1 ± 1.6 G6: 18 ± 1.5 ABC-Stereotypic Behavior G1: 11.9 ± 0.9 G2: 11.4 ± 0.8 G3: 11.6 ± 0.8 G4: 10.7 ± 0.9 G5: 10.7 ± 0.8 G6: 10.7 ± 0.8 ABC-Hyperactivity G1: 34.1 ± 1.4 G2: 33.1 ± 1.4	**Change scores** ABC-Irritability G1: -12.9 ± 1.4 G2: -12.4 ± 1.4 G3: -13.2 ± 1.3 G4: -14.4 ± 1 G5: -5 ± 1.4 G6: -8.4 ± 1.4 G1 vs G6, p<0.05 G2 vs G6, p<0.05 G3 vs G6, p<0.05 G4 vs G6, p<0.05 ABC-Social Withdrawal/Lethargy G1: -7.9 ± 1.2 G2: -5.8 ± 1.2 G3: -4.9 ± 1.1 G4: -7.9 ± 1.1 G5: -62 ± 1.1 G6: -5.2 ± 1.2 G5 vs G6, p=ns ABC-Stereotypic Behavior G1: -4.8 ± 0.6 G2: -4.5 ± 0.7 G3: -4.2 ± 0.6 G4: -4.5 ± 0.7

	G3: 33.7 ± 1.3 G4: 32.2 ± 1.4 G5: 34.7 ± 1.4 G6: 31 1. ± 4 ABC-Inappropriate Speech G1: 7 ± 0.6 G2: 5.8 ± 0.6 G3: 6.8 ± 0.5 G4: 6.3 ± 0.5 G5: 7 ± 0.6 G6: 5.9 ± 0.6	G5: -2 ± 0.6 G6: -1.8 ± 0.7 G1 vs G6, p<0.05 G2 vs G6, p<0.05 G3 vs G6, p<0.05 G4 vs G6, p<0.05 ABC-Hyperactivity G1: 12.7 ± 1.5 G2: -14 ± 1.6 G3: -13.3 ± 1.5 G4: -16.3 ± 1.6 G5: -2.8 ± 1.5 G6: -7.7 ± 1.7 G1 vs G6, p<0.05 G2 vs G6, p<0.05 G3 vs G6, p<0.05 G4 vs G6, p<0.05 ABC-Inappropriate Speech G1: -2.5 ± 0.4 G2: -2 ± 0.5 G3: -1.8 ± 0.4 G4: -2.3 ± 0.4 G5: -0.4 ± 0.4 G6: -1.1 ± 5 G4 vs G6, p<0.05
Findling 2014[46] RCT G1: Aripiprazole (2-15 mg/day), 41/22 G2: Placebo (NA), 44/19 16 weeks/EOT Low RoB	ABC-I – adjusted mean score NR CGI - improvement scale NR	**Change scores** ABC- I G1: 5.2 G2: 9.6 G1 vs G2: p=ns ABC- Hyperactivity G1: 5.0 G2: 10.3 G1 vs G2: p=0.041 ABC- Stereotypy G1: 0.8 G2: 2.8 G1 vs G2: p=0.018 ABC- Inappropriate speech G1: 0.6 G2: 2.1 G1 vs G2: p=0.013 ABC- Social withdrawal G1: 0 G2: 1.5 G1 vs G2: p=ns CGI- I G1: 4.2 G2: 4.8 G1 vs G2: p=ns

ABC = Aberrant Behavior Checklist; CGI-I - Clinical Global Impression Scale Improvement, EOT = End Of Treatment; G = Group; kg = Kilograms; mg = Milligrams; NR = Not Reported; NS = Not Significant; RCT = Randomized Controlled Trial; RoB = Risk of Bias; SD = Standard Deviation

Studies Comparing Risperidone and Aripiprazole

Two small studies comparing these agents reported no significant group differences in measures of challenging behavior or general improvement. One 8-week RCT (low risk of bias) reported improvements in ABC-Irritability, Hyperactivity, Lethargy, Stereotypy, and Inappropriate speech scores in both risperidone and aripiprazole arms.[71] Most patients were much or minimally improved on the CGI-Improvement scale, but differences between the groups on all of these scales were not statistically significant. Another retrospective cohort study (moderate risk of bias), which primarily reports weight change (see Harms section below), noted no significant group differences in mean CGI-Improvement scores (risperidone=3.2±1.2, aripiprazole=2.9±1.2, p=0.32) after treatment with risperidone (mean treatment duration=2.37±2.55 years) or aripiprazole (mean treatment duration=1.47±1.21 years).[102] The study did not report CGI scores at baseline so the magnitude of change cannot be assessed.

Table 9. Key outcomes in studies comparing risperidone and aripiprazole

Author, Year, Study Design Groups (Dose), N Enrollment / N Final Treatment Duration/Follow-Up Time Point Post-Treatment Risk Of Bias	Baseline Scores, Mean ±SD	Post-Treatment Scores, Mean ± SD
Ghanizadeh 2014[71] RCT G1: Aripiprazole (1.25-10 mg/day), 29/29 G2: Risperidone (0.25-3 mg/day), 30/30 2 months/EOT Low RoB	ABC-Irritability G1: 26.2 ± 4.1 G2: 21.5 ± 7.4 ABC-Hyperactivity G1: 37.1 ± 7 G2: 36 ± 6.2 ABC-Lethargy G1: 27.5 ± 8.4 G2: 25.3 ± 8.9 ABC-Stereotypy G1: 13.6 ± 5.7 G2: 13.2 ± 4.2 ABC-Speech G1: 8.6 ± 3.1 G2: 8.9 ± 3.6	**EOT** ABC-Irritability G1: 14.6 ± 5.5 G2: 12.5 ± 5.4 G1 vs G2: p=ns ABC-Hyperactivity G1: 21.1 ± 9 G2: 19.1 ± 6.1 G1 vs G2: p=ns ABC-Lethargy G1: 17.3 ± 7.4 G2: 16.1 ± 6.9 G1 vs G2: p=ns ABC-Stereotypy G1: 8.2 ± 5 G2: 7.4 ± 3.9 G1 vs G2: p=ns ABC-Speech G1: 4.9 ± 2.3 G2: 5.7 ± 3.1 G1 vs G2: p=ns CGI-Improvement, n Much improved G1: 9 G2: 5 Minimally improved G1: 7

		G2: 12 No change G1: 5 G2: 8 Minimally worse G1: 3 G2: 2 G1 vs G2: p=ns

ABC = Aberrant Behavior Checklist; CGI- Clinical Global Impression Scale, EOT = End Of Treatment; ES = Effect Size; G = Group; mg = Milligrams; N = number; NS = Not Significant; RCT = Randomized Controlled Trial; RoB = Risk of Bias; SD = Standard Deviation

Harms of Antipsychotics

Risperidone. Table 10 outlines harms reported in study arms addressing risperidone. Among clinically important harms, appetite increase occurred in over 70 percent of children and extrapyramidal symptoms in 36 percent. Gastrointestinal symptoms (including constipation, diarrhea, and abdominal pain) occurred in nearly all children in the 8 week RCT, and more than 25 percent across phases experienced anxiety and hypersalivation. Across studies, six children withdrew due to adverse events.

Some studies reported comparative analyses of harms data: In the RUPP extension study urinary problems occurred in 19.6 percent of patients who took risperidone, and 0% of patients that did not (p=0.01). Excessive appetite occurred in 42.1 percent of patients who took risperidone and 20 percent of those who did not (p=ns). In another RCT comparing risperidone doses and placebo, the incidence of treatment-emergent adverse events was higher in the high dose group compared with the low dose group and placebo.[104, 105] In combining high and low dose groups, the most common events included increased appetite (26%), sedation (15%), somnolence (11%) and weight increase (11%). Sedation, somnolence and increased appetite occurred with twice the frequency in the high dose group than in the low dose group.

In an analysis of prolactin changes in children participating in the RUPP trial, serum prolactin increased significantly from baseline in children taking risperidone at 8 weeks and 6 months, though concentrations were lower at 6 months than at weeks.[41] Levels were higher in treated children compared with those in the placebo group. In the 20 treated children with measurements at 8 weeks, 6 months, and ~22 months, levels were significantly elevated at each time point compared with baseline, but levels at 22 months were significantly lower than those at 6 months (p=0.016). While these elevations represented 2 to 4 fold increases in prolactin, no children reported clinical complaints such as galactorrhea, gynecomastia, or menstrual changes. Another study reported no significant differences in weight change between risperidone and placebo groups (increase of 17% in the risperidone group and 9.3% in placebo).[60]

Table 10. Harms/adverse events reported by study phase in RUPP risperidone studies

Treatment Duration Adverse Event	Risperidone: 8 weeks[34] (n=49)	Risperidone: 6 months[36] (n=95)	Risperidone: 21.4 months (mean)[28] (n=84)	Placebo: 8 weeks[34] (n=51)
N (%)				
Accidental injury	NR	2 (3.2)	NR	NR
Agitation/nervousness/ restlessness	3 (6)	1 (1.6)	NR	3 (6)
Anxiety	12 (24)	3 (4.8)	7 (12.3)	10 (20)
Appetite change	NR	NR	4 (7.1)	
Appetite increase	36 (73)	5 (7.9)	24 (42.1)	15 (29)

Appetite decrease	3 (6)	NR	NR	5 (10)
Depression/sadness	NR	1 (1.6)	NR	NR
Dizziness	8 (16)	NR	NR	2 (4)
Drooling/increased saliva	13 (27)	2 (3.2)	10 (17.5)	3 (6)
Dry mouth	9 (18)	NR	6 (10.6)	5 (10)
EPS/impaired movement	18 (36)	3 (4.8)	NR	5 (10)
GI symptoms	48 (98)	7 (11.1)	25 (44.2)	43 (86)
Headache	9 (18)	2 (3.2)	NR	6 (12)
Heart rate changes	6 (12)	NR	NR	1 (2)
Infection/fever/cold/ congestion symptoms	35 (71)	18 (28.6)	7 (12.5)	23 (45)
Insomnia	7 (14)	3 (4.8)	NR	15 (29)
Skin changes	11 (22)	3 (4.8)	3 (5.4)	7 (14)
Sleep changes	11 (22)	NR	6 (10.5)	9 (18)
Fatigue	23 (47)	1 (1.1)	NR	6 (12)
Drowsiness	16 (32.6)	2 (4.1)	13 (15.5)	NR
Thirst	6 (12)	NR	NR	5 (10)
Urinary changes	15 (31)	3 (4.8)	11 (19.6)	15 (29)

EPS=extrapyramidal symptoms; GI=gastrointestinal; N=number; NR=not reported

Harms reported in other risperidone studies were similar (Table 11).

Table 11. Harms/adverse effects in other studies of risperidone

Harm/Adverse Event*	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Risperidone, 1-1.17mg/day		
Agitation/nervousness/restlessness[71]	1 (3/30)	10%
Appetite decrease[67, 68, 71]	2 (8/70)	10%-13.3%
Appetite increase[67, 68, 71]	2 (21/70)	22.5%-40%
Challenging behavior[67, 68]	1 (5/40)	12.5%
Dizziness[71]	1 (3/30)	10%
Drooling/increased saliva[67, 68, 71]	2 (16/70)	10%-40%
EPS/impaired movement[60, 67, 68, 71]	3 (24/89)	3.3%-16%
GI symptoms[67, 68, 71]	2 (25/70)	3.3%-20%
Headache[67, 68]	1 (5/40)	12.5%
Heart rate changes[67, 68, 71]	2 (6/70)	3.3%-12.5%
Infection/fever/cold/congestion symptoms[67, 68]	1 (44/40)	10%-37.5%
Insomnia[67, 68]	1 (6/40)	15%
Somnolence[60, 67, 68, 71]	3 (46/89)	10%-72.5%
Urinary changes[71]	1 (2/30)	6.7%
Weight gain[67, 68]	1 (4/40)	10%
Risperidone, 1.25-1.75mg/day		
EPS/impaired movement[73, 74]	1 (7/31)	22.6%
GI[73, 74]	1 (4/25)	16%
Infection/fever/cold/congestion symptoms[73, 74]	1 (7/25)	28%
Pain[73, 74]	1 (2/25)	8%
Somnolence[73, 74]	1 (20/31)	64.5%
Risperidone, 0.125-0.175mg/day		
Appetite increase[73, 74]	1 (2/24)	8%
EPS/impaired movement[73, 74]	1 (2/24)	8%
GI symptoms[73, 74]	1 (4/24)	16.7%
Infection/fever/cold/congestion symptoms[73, 74]	1 (8/24)	33.3%
Insomnia[73, 74]	1 (2/24)	8%
Somnolence[73, 74]	1 (3/30)	10%
Placebo		
Agitation/nervousness/restlessness[73, 74]	1 (2/30)	7%
Appetite increase[67, 68, 73, 74]	2 (11/69)	15.9%

Harm/Adverse Event*	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Challenging behavior[73, 74]	1 (3/35)	9%
EPS/impaired movement[67, 68, 73, 74]	2 (4/58)	6.9%
GI[46, 67, 68, 73, 74]	3 (20/117)	17.1%
Headache[67, 68, 73, 74]	2 (9/74)	12.2%
Infection/fever/cold/congestion symptoms[46, 67, 68, 73, 74]	3 (35/112)	31.3%
Insomnia[67, 68, 73, 74]	2 (9/74)	12.2%
Somnolence[67, 68, 73, 74]	2 (15/74)	20.3%
Urinary changes[73, 74]	1 (2/30)	7%

*Harms reported by more than one participant

Aripiprazole. Table 12 outlines harms reported in study arms addressing aripiprazole. Harms reported across studies included weight gain, appetite changes, lethargy, and extrapyramidal symptoms. Across studies 34 children withdrew due to adverse events. Some studies reported comparative analyses of harms data: in an analysis of harms reported in two 8-week trials[20, 21] of aripiprazole vs. placebo, the percentage of patients who discontinued due to at least adverse event with aripiprazole was 10.4 percent compared with 6.9 percent in the placebo groups.[19] The most common adverse events reported in the aripiprazole groups compared with placebo were: sedation (10.4% vs. 4.0%), fatigue (16.5% vs. 2.0%), vomiting (13.7% vs 6.9%), increased appetite 12.7% vs. 6.9%), somnolence (10.4% vs. 4.0%), and tremor (9.9% vs. 0.0%). Younger children (6-12 years) had a higher group rate of salivary hypersecretion in the aripiprazole group (6.6% vs 0% in the placebo group), but older children (13-17 years) did not. The majority of adverse events had a peak incidence of onset at week 1 or 2, except for nasopharyngitis and tremor, which had a peak incidence at week 3, extrapyramidal disorder and aggression at week 4, drooling at week 5, diarrhea at weeks 2 and 5, enuresis and upper respiratory tract infection at week 6 and cough at week 7. Investigators rated most adverse events as mild or moderate. Most of the adverse events rated as severe were in the younger (6-12 years) subgroup, with one event of severe fatigue in the 13-17 age group. Fatigue was the only adverse event that showed a statistically significant dose-response relationship, with 3.8 percent reporting fatigue at 5mg/d, 22 percent at 10mg/d and 18.5 percent at 15mg/d. The adjusted mean change (last observation carried forward) in body weight was higher in the aripiprazole group (1.6 kg) than the placebo group (0.4 kg) ($p<0.001$). The median change in BMI (0.7 vs. 0.2 kg/m2) was also higher in the aripiprazole group than the placebo group. Extrapyramidal-related adverse events were also more frequent in the aripiprazole group (20.8% vs. 9.9%). The most common extrapyramidal-related adverse events were tremor (9.9% vs 0% in placebo) and extrapyramidal disorder (6.1% vs 0% in placebo).

In the 52-week open label extension of these trials, 286 of 330 patients (86.7%) reported adverse events.[18] Discontinuations were significant in the three groups: 36 percent of de novo patients discontinued, 47.1 percent of prior placebo patients discontinued, and 38.5 percent of prior aripiprazole patients discontinued. Common reasons for discontinuation were adverse events, withdrawal of consent, lost to follow up and lack of efficacy. The most common adverse events reported from the three groups combined were weight increased (23%), vomiting (18.8%), nasopharyngitis (13.3%), increased appetite (13.0%), pyrexia (11.8%), upper respiratory tract infection (11.5%), insomnia (10.0%), headache (9.7%), cough (9.4%), diarrhea (9.1%), aggression (8.8%), sedation (8.2%) and fatigue (7.0%). Drooling, agitation, epistaxis, ear infection, nasal congestion, sinusitis, and constipation were also reported in >5% of patients.

In another RCT, 56.4 percent of children in the aripiprazole group reported a treatment-emergent adverse event compared with 32.6 percent of the placebo group. Adverse events reported by at least 5 percent of participants and at least twice the rate of placebo included upper respiratory tract infections (10.3% for aripiprazole vs. 2.3% for placebo), constipation (5.1% for aripiprazole vs. 0% for placebo), and movement disorder (5.1% for aripiprazole vs. 0% for placebo, p=NR). Weight change was 0.15 standard deviations greater in the aripiprazole group compared with placebo (mean gain of 2.2kg vs. 0.6kg, p=0.001). Fasting metabolic measurements were not different between groups, but the mean change in prolactin showed a difference of -4.8 (95% CI: -6.8 to -2.9; -0.2ng/ml for aripiprazole and 4.6ng/ml for placebo).[46]

Table 12. Harms/adverse events reported by study phase in aripiprazole "family" studies

Treatment Duration Adverse Event	Aripiprazole: Fixed Dose+Flexible Dose, 8 weeks[19] (n=212*)	Aripiprazole: 52 week open label extension[18] (n=330)	Placebo: 8 weeks[19] (n=101)
	N (%)		
Agitation/nervousness/ restlessness	NR	21 (6.4)	NR
Anxiety	NR	13 (3.9)	NR
Appetite increase	27 (12.7)	43 (13.0)	7 (6.9)
Appetite decrease	14 (6.6)	15 (4.5)	2 (2.0)
Challenging behavior	6 (2.8)	44 (13.3)	7 (6.9)
Drooling/increased saliva	31 (14.7)	22 (6.7)	1 (1.0)
Epistaxis	NR	21 (6.4)	NR
EPS/impaired movement	34 (16.0)	16 (4.8)	0
GI symptoms	56 (26.4)	132 (40.0)	20 (19.8)
Headache	16 (7.5)	32 (9.7)	10 (9.9)
Infection/fever/cold/congestion symptoms	56 (26.4)	220 (70.8)	16 (16.0)
Insomnia	11 (5.2)	33 (10.0)	11 (10.9)
Lethargy	10 (4.7)	10 (3.0)	0
Menstrual	NR	1 (2.3)	NR
Skin changes	NR	15 (4.5)	NR
Somnolence	101 (47.7)	63 (19.1)	10 (10.0)
Urinary changes	7 (3.3)	15 (4.5)	5 (5.0)
Weight gain	NR	76 (23.0)	NR

*Study reported only events occurring in at least 5% of participants. EPS=extrapyramidal symptoms; GI=gastrointestinal; N=number

Harms reported in other studies of aripiprazole were similar (Table 13).

Table 13. Harms/adverse effects in other studies of aripiprazole

Harm/Adverse Event*	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Agitation/nervousness/restlessness[71]	1 (3/29)	10.3%
Appetite decrease[71]	1 (6/29)	20.7%
Appetite increase[71]	1 (10/29)	34.5%
Drooling/increased saliva[71]	1 (9/29)	31%
Dry mouth[71]	1 (2/29)	6.9%
EPS/impaired movement[46, 71]	2 (14/68)	20.6%
GI symptoms[46, 71]	2 (14/68)	20.6%
Heart rate changes[71]	1 (2/29)	6.9%
Infection/fever/cold/congestion symptoms[46]	1 (4/39)	10.3%
Skin changes[71]	1 (4/29)	13.8%
Somnolence[71]	1 (11/29)	37.9%

*Harms reported by more than one participant. EPS=extrapyramidal symptoms; GI=gastrointestinal

Risperidone vs. Aripiprazole. One retrospective cohort study compared these agents in 142 children, all of whom were relatively overweight at baseline (BMI Z scores of 0.67±1.44 in children receiving risperidone and 0.64±1.94 in those receiving aripiprazole, p=ns).[102] Children taking aripiprazole were older than those taking risperidone at baseline (9.74±3.46 years vs. 8.41±3.59, p=0.03), and children taking risperidone had a longer mean treatment duration (2.37±2.55 vs. 1.47±1.21 years, p=0.01). Other demographic characteristics and use of concomitant medications did not differ significantly between groups. Both groups gained weight over time (significant increases in BMI and BMI Z-scores in each group), with no significant group differences in BMI change per year of treatment (2.36±3.80 in risperidone group vs. 2.05±5.02 for aripiprazole, p=0.68) or BMI Z-score change per year of treatment (0.53±1.21 for risperidone vs. 0.56±2.21 for aripiprazole, p=0.91). Investigators note that the study was underpowered to detect differences in Z-scores. In another RCT, four children withdrew from the study because of adverse events.[71]

Studies of Stimulants

Key Points

- Both RCTs addressing methylphenidate (MPH) reported significant improvements in hyperactivity in children treated with medium to high doses compared with placebo. One RCT also noted significant treatment effects on inattention. Harms were frequent and included challenging behavior, anxiety, and appetite changes.
- One RCT of guanfacine reported significant improvements in hyperactivity in treated participants compared with the placebo group and no significant group differences in measures of cognitive skills. Harms included drowsiness and fatigue.
- Strength of evidence for effects of MPH on hyperactivity was low as studies were small and short term. Strength of evidence was also low for no effect on oppositional behavior and low for association with significant harms given the small sample and insufficient for effects on social communication.
- Strength of evidence for guanfacine was insufficient given the small sample size and short-term assessment in one RCT.

Overview of the Literature

We identified three RCTs (reported in multiple publications) addressing stimulant medications.[24-27, 53, 66] One study, conducted by the RUPP network, was included in our 2011 review.[24-27] Studies included a total of 152 children between the ages of 5 and 14. All three RCTs had low risk of bias, and all were conducted in the United States. Studies addressed MPH compared with placebo[24-27, 53] or guanfacine compared with placebo.[66] Treatment duration ranged from 4 to 8 weeks, with one trial including a 4-week randomized phase and an 8-week open label continuation phase.[24-27] No studies were industry-funded.

Detailed Analysis

Studies of MPH and guanfacine both reported improvements in hyperactivity and other challenging behaviors with treatment compared with placebo (Table 33). Significant side effects were associated with MPH including aggressive behavior and appetite changes.

Methylphenidate. The RUPP Autism Network's double-blind cross-over trial of MPH compared a one-day placebo followed by two days at each of three (low, medium, high) test doses of MPH;[25-27] doses ranged from 7.5 mg/day to 50.0 mg/day. Children tolerating MPH (n=66) moved on to a 4-week, double-blind crossover phase. Children with a positive response in the double blind phase (n=34) completed an 8-week open-label continuation phase at their best dose. The primary outcome measure was hyperactivity as assessed by the ABC teacher-rated hyperactivity subscale; secondary measures included the ABC parent-rated hyperactivity subscale. Blinded clinicians also assessed participants using the CGI-Irritability scale; investigators combined this subscale and the ABC parent and teacher rated hyperactivity subscales to assess response (Table 14).

In the double-blind crossover phase, all MPH doses demonstrated effects that were statistically superior to placebo, and effect sizes favored the medium dose for parent ratings and high dose for teacher ratings. Parent-rated lethargy/ social withdrawal significantly worsened during the high dose of MPH compared with placebo. Parent-rated stereotypy and inappropriate speech scores improved significantly at the medium dose of MPH compared with placebo. Hyperactivity/impulsivity also improved more with the medium and high MPH doses than at the low dose. Significantly more joint attention behaviors occurred in the intervention group both at the best MPH dose and at the low dose compared with placebo. Self-regulation, as assessed in a "competing demands" task, improved in low dose as well as in medium dose MPH compared with placebo, and neutral affect significantly increased at the medium and high dose, which could be either beneficial, in the case of children with a labile mood, or damaging, in the case of children with flattened affect due to a medication side effect.[25-27]

In another 4-week RCT comparing extended release MPH and placebo in children with ASD and significant Attention Deficit Hyperactivity Disorder (ADHD) symptoms with higher IQs (mean=85±16.8), children in the treatment group received extended release MPH (low, medium, or high doses) in the morning and immediate release MPH in the afternoon.[53] Parent-rated measures of attention, ASD symptoms, hyperactivity and impulsivity improved significantly more at higher doses compared with lower doses and with placebo, and teachers reported significant improvements in hyperactivity, inattention and impulsivity at higher doses compared with lower doses and with placebo. Teachers (but not parents) also reported significant improvements in oppositional behavior with high dose MPH compared with placebo. Neither teachers or parents reported significant group differences in measures of emotional lability or social communication. Clinician-rated severity was significantly improved at all MPH doses compared with placebo.

Guanfacine. One RCT evaluating extended release guanfacine included mostly males with ASD and hyperactivity, impulsiveness, and distractibility and reported significant improvements in hyperactivity (effect size=1.67, $p<0.001$) in the treated group compared with placebo.[66] Cognitive tests of working memory did not differ between groups.

Table 14. Key outcomes in studies of stimulants

Author, year, Study Design Groups (dose), N enrollment / N final Treatment Duration Risk of Bias	Outcome measure/Baseline scores, mean ±SD	Outcome measure/Post-treatment scores, mean ± SD

Scahill 2015[66] RCT G1: Extended-Release Guanfacine (1-3 mg/day), 30/26 G2: Placebo (NA), 32/28 8 weeks/EOT Low RoB	ABC-Irritability G1: 20.30 ± 9.4 G2: 18.06 ± 9.77 ABC-Social withdrawal G1: 13.60 ± 9.43 G2: 12.06 ± 9.29 ABC-Stereotypy G1: 8.53 ± 5.69 G2: 9.31 ± 5.56 ABC-Hyperactivity G1: 34.40 ± 5.35 G2: 34.25 ± 6.97 ABC-Inappropriate speech G1: 6.33 ± 3.53 G2: 6.84 ± 3.38	ABC-Irritability G1: 13.5 G2: 16.1 G1 vs G2: p=ns ABC-Social withdrawal G1: 9.8 G2: 8.6 G1 vs G2: p=ns ABC-Stereotypy G1: 3.6 G2: 5.9 G1 vs G2: p=0.02 ABC-Hyperactivity G1: 19.3 G2: 29.7 G1 vs G2: p<0.001 ABC-Inappropriate speech G1: 4.2 G2: 5.99 G1 vs G2: p=0.004
McCracken 2014[27_4421_4386_380] RCT (crossover) Total N=66 G1: Methylphenidate - low dose (0.125 mg/kg), 66/45 G2: Methylphenidate - medium dose (0.250 mg/kg), 66/52 G3: Methylphenidate - high dose 0.500 mg/kg (), 66/33 G4: Methylphenidate - optimal dose (NR), 66/58 G5: Placebo (NA), 66/46 13 weeks/EOT Low RoB	Overall ratings: CGI severity sub-scale rating, n (%): Moderately ill: 20 (30.3) Markedly ill: 35 (52.0) Severely ill: 11 (16.7) ABC score, parent-rated, mean ± SD (range):† Irritability: 16.9 ± 10.1 (0-41) Lethargy/social withdrawal: 12.1 ± 8.9 (0-33) Stereotypy: 7.6 ± 5.9 (0-21) Hyperactivity: 33.2 ± 8.7 (2-47) Inappropriate speech: 6.0 ± 4.1 (0-12) ABC score, teacher-rated, mean ± SD (range):† Irritability: 16.1 ± 9.4 (0-43) Lethargy/social withdrawal: 15.5 ± 10.9 (0-42) Stereotypy: 7.6 ± 5.1 (0-19) Hyperactivity: 30.9 ± 7.9 (16-45) Inappropriate speech: 5.8 ± 3.6 (0-12)	ABC-hyperactivity subscale score, mean ± SD: Parent-rated: G1: 23.0 ± 11.29 G2: 20.6 ± 10.27 G3: 22.1 ± 9.67 G4: 17.2 ± 9.87 G5: 26.0 ± 9.90 G1/G5: P = 0.03 (es = 0.29) G2/G5: P < 0.001 (es = 0.54) G3/G5: P = 0.003 (es = 0.40) G4/G5: P < 0.001 (es = 0.89) Teacher-rated: G1: 22.9 ± 12.84 G2: 23.6 ± 12.53 G3: 20.3 ± 11.94 G4: 20.1 ± 12.40 G5: 26.0 ± 11.66 G1/G5: P = 0.03 (es = 0.25) G2/G5: P = 0.008 (es = 0.20) G3/G5: P = 0.002 (es = 0.48) G4/G5: P < 0.001 (es = 0.48)
Pearson 2013[53] RCT (crossover) G1: Methylphenidate - low dose (0.125 mg/kg), 24/24 G2: Methylphenidate - medium dose (0.250 mg/kg), 24/24	ABC NR	**EOT** Parent Ratings ABC-Irritability G1: 10 ± 9.2 G2: 8.2 ± 8.1 G3: 7.2 ± 6.9

G3: Methylphenidate - high dose (0.500 mg/kg), 24/24 G4: Placebo, 24/24 4 weeks/EOT Low RoB		G4: 12.6 ± 10.4 ABC-Social Withdrawal/Lethargy G1: 7.3 ± 5.6 G2: 8.1 ± 5.9 G3: 8.5 ± 6.6 G4: 9.3 ± 8.1 ABC-Stereotypy G1: 4.3 ± 4.5 G2: 4 ± 3.8 G3: 3.5 ± 3.8 G4: 4.9 ± 5.4 ABC-Hyperactivity G1: 18.1 ± 10.5 G2: 14.5 ± 7.7 G3: 14.5 ± 9.2 G4: 24.1 ± 13 ABC-Inappropriate Speech G1: 4.3 ± 3.2 G2: 4 ± 3.1 G3: 3.9 ± 3.1 G4: 5.2 ± 3.1 CGI-Severity (clinician 1) G1: 4 ± 0.81 G2: 3.8 ± 0.82 G3: 3.8 ± 0.74 G4: 4.8 ± 0.61 CGI-Improvement (clinician 1) G1: 2.8 ± 1.3 G2: 2.4 ± 1.3 G3: 2.1 ± 1.2 G4: 4 ± 0.81 CGI-Severity (clinician 2) G1: 4 ± 0.72 G2: 4 ± 0.62 G3: 3.9 ± 0.74 G4: 4.7 ± 0.76 CGI-Improvement (clinician 2) G1: 2.8 ± 1.4 G2: 2.6 ± 1.3 G3: 2 ± 1 G4: 4.1 ± 0.95

ABC = Aberrant Behavior Checklist; CGI = Clinical Global Impressions Scale; EOT = End of Treatment; ES = Effect Size; G = Groups; kg = Kilograms; mg = Milligrams; NA = Not Applicable; NS = Not Significant; RCT = Randomized Controlled Trial; RoB = Risk of Bias; SD = Standard Deviation

Harms of Stimulants

MPH was associated with changes in appetite and challenging and repetitive behavior at all doses (rates ranging from 5% to 50%) and with anxiety and insomnia (at lower doses). Five (out of 24) children discontinued an afternoon dose of medication because of irritability in one study,[53] and 13 of 72 discontinued a second RCT due to irritability (n=6) or other adverse effects.[24-27] Guanfacine was fairly well tolerated: four children withdrew from the trial (2 for adverse events and 2 for lack of efficacy), and one child had severe aggressive behavior that resulted in patient psychiatric hospitalization. Other side effects included fatigue, decreased appetite, drowsiness, dry mouth, emotional lability, and anxiety. Heart rate and blood pressure decreased in treated patients with attenuation over time. Table 15 outlines harms.

Table 15. Harms/adverse effects in studies of stimulants

Harm/Adverse Event*	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Methylphenidate (0.125-0.21 mg/kg/day)		
Anxiety[24-27, 53]	2 (7/90)	4.6%-17%
Appetite decrease[24-27, 53]	2 (10/90)	4.6%-29%
Challenging behavior[24-27, 53]	2 (18/90)	15.2%-33%
Depression/sadness[24-27, 53]	2 (3/90)	1.5%-8%
EPS/impaired movement[24-27, 53]	2 (6/90)	4.6%-8%
GI symptoms[24-27, 53]	2 (6/90)	4%-7.6%
Headache[24-27, 53]	2 (4/90)	3.0%-8%
Heart rate changes[24-27, 53]	2 (3/90)	4%-4.6%
Insomnia[24-27, 53]	2 (14/90)	10.6%-50%
Repetitive language[53]	1 (13/24)	54.2%
Repetitive behavior[24-27, 53]	2 (20/90)	3%-46%
Somnolence[24-27, 53]	2 (2/90)	1.5%-4%
Withdrawal[24-27]	1 (2/66)	3.0%
Methylphenidate (0.24-0.35 mg/kg/day)		
Anxiety[24-27, 53]	2 (7/90)	1.5%-25%
Appetite Decrease[24-27, 53]	2 (25/90)	24.2%-38%
Challenging behavior[24-27, 53]	2 (25/90)	25.7%-33%
Depression/sadness[24-27, 53]	2 (7/90)	4.6%-17%
Dry mouth[53]	1 (2/24)	8%
EPS/impaired movement[24-27, 53]	2 (3/90)	1.5%-8%
GI symptoms[24-27, 53]	2 (9/90)	7.6%-17%
Headache[24-27, 53]	2 (5/90)	1.5%-17%
Heart rate changes[24-27, 53]	2 (1/90)	4%-4.6%
Insomnia[24-27, 53]	2 (14/90)	18.2%-50%
Hair/skin pulling[53]	1 (3/24)	12.5%
Repetitive language[53]	1 (12/24)	50%
Repetitive behavior[24-27, 53]	2 (16/90)	6%-50%
Self-injury behavior[24-27]	1 (3/66)	4.6%
Somnolence[24-27, 53]	2 (5/90)	4%-6.1%
Staring[53]	1 (2/24)	8%
Withdrawal[24-27]	1 (4/66)	6.1%
Methylphenidate (0.27-0.50 mg/kg/day)		
Anxiety[24-27, 53]	2 (6/74)	8%
Appetite decrease[24-27, 53]	2 (21/74)	24%-38%
Challenging behavior[24-27, 53]	2 (17/74)	20%-29%
Depression/sadness[24-27, 53]	2 (5/74)	4%-8%
EPS/impaired movement[24-27, 53]	2 (3/74)	2%-8%
GI[24-27, 53]	2 (10/74)	12%-12.2%
Headache[24-27, 53]	2 (4/74)	4%-6%
Insomnia[24-27, 53]	2 (21/74)	24%-38%
Hair/skin pulling[53]	1 (2/24)	8.3%
Repetitive language[53]	1 (9/24)	37.5%
Repetitive behavior[24-27, 53]	2 (12/74)	6%-37%
Self-injury behavior[24-27]	1 (3/50)	6.0%
Somnolence[24-27, 53]	2 (2/74)	1.5%-8%
Withdrawal[24-27]	1 (2/50)	4%

Harm/Adverse Event*	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Guanfacine-extended release (1-3 mg/day)		
Anxiety[66]	1 (9/30)	30%
Appetite Increase[66]	1 (2/30)	6.7%
Appetite Decrease[66]	1 (13/30)	43.3%
Challenging behavior[66]	1 (18/30)	60%
Depression/sadness[66]	1 (4/30)	13.3%
Dizziness[66]	1 (3/30)	10%
Dry mouth[66]	1 (12/30)	40%
Energy level changes[66]	1 (9/30)	30%
EPS/impaired movement[66]	1 (4/30)	13.3%
Eye/vision changes[66]	1 (2/30)	6.7%
GI symptoms[66]	1 (24/30)	80%
Headache[66]	1 (9/30)	30%
Infection/fever/cold/congestion symptoms[66]	1 (5/30)	16.7%
Insomnia[66]	1 (9/30)	30%
Nightmares[66]	1 (2/30)	6.7%
Repetitive behaviors or language[66]	1 (6/30)	20%
Self-injury behavior[66]	1 (3/30)	10%
Silliness[66]	1 (3/30)	10%
Skin changes[66]	1 (2/30)	6.7%
Sleep changes[66]	1 (3/30)	10%
Somnolence[66]	1 (19/30)	63.3%
Urinary changes[66]	1 (2/30)	6.7%
Placebo		
Anxiety[24-27, 53, 66]	3 (7/122)	3.0%-17.0%
Appetite Increase[66]	1 (2/32)	6.3%
Appetite Decrease[24-27, 53, 66]	3 (5/122)	3.0%-6.3%
Challenging behavior[24-27, 53, 66]	3 (30/122)	3.0%-53.1%
Depression[53, 66]	2 (7/56)	3.1%-13%
Dizziness[66]	1 (2/32)	6.3%
Energy level changes[66]	1 (6/32)	18.8%
EPS/impaired movement[24-27, 53, 66]	3 (4/122)	1.5%-13%
GI[24-27, 53, 66]	3 (18/122)	7.6%-34.4%
Headache[53, 66]	2 (7/56)	12.5%
Infection/fever/cold/congestion symptoms[66]	1 (7/32)	21.9%
Insomnia[24-27, 53, 66]	3 (10/122)	1.5%-21%
Hair/skin pulling[53, 66]	2 (6/56)	4%-9.4%
Repetitive language[53]	1 (12/24)	50%
Repetitive behavior[24-27, 53, 66]	3 (25/122)	3%-50%
Self-injury behavior[24-27]	1 (2/66)	3%
Silliness[66]	1 (5/32)	15.6%
Skin changes[66]	1 (4/32)	12.5%
Sleep changes[66]	1 (2/32)	6.3%
Somnolence[53, 66]	1 (7/56)	12.5%
Staring[53]	1 (4/24)	17%
Urinary changes[66]	1 (2/32)	6.3%

*Harms reported by more than one participant. EPS = Extrapyramidal Symptoms; GI = Gastrointestinal; mg = Milligrams; n - Number

Studies of Norepinephrine Reuptake Inhibitors

Key Points

- Studies of atomoxetine reported promising findings related to improvements in hyperactivity in children with ASD and ADHD with moderate adverse effects.
- Strength of the evidence was low for positive effects of atomoxetine compared with placebo on hyperactivity and insufficient for effects on inattention as studies reported inconsistent findings.

Overview of the Literature

We identified two RCTs (reported in multiple publications) addressing the norepinephrine reuptake inhibitor atomoxetine.[55-58, 100] Studies were conducted in the Netherlands[55-58] and the United States[100] and had low[55-58] and moderate risk of bias.[100] Studies included a total of 113 children between 6 and 17 years old with ASD and Attention Deficit Hyperactivity Disorder (ADHD) symptoms. Treatment duration ranged from 6 to 28 weeks (one study included a 20-week open label extension,[55-58]) with followup immediately after the end of treatment in both studies. Both studies were manufacturer-funded.

Detailed Analysis

Two RCTs of atomoxetine reported significant treatment-related improvements compared with placebo that were maintained over 20 weeks of open label, uncontrolled treatment in one study; inattention was significantly improved in one study, and side effects were generally moderate (Table 16). In one low risk of bias RCT (reported in multiple publications), the initial study phase included participants with ASD and ADHD and compared atomoxetine with placebo.[55-58] After 8 weeks of treatment, the atomoxetine group improved significantly more on the clinician-rated ADHD Rating Scale total score and on the inattention and hyperactivity/impulsivity subscales (p values $\leq$ 0.003). Nine of 48 treatment group participants and 4/49 placebo group were considered very much or much improved in the CGI-ADHD-I (p=ns). Scores on only the hyperactivity subscale of the Conners Teacher Rating Scale were significantly different between groups (difference in least square means: -2.0 [95% CI: -3.7 to -0.3], p=0.02). Children in the atomoxetine arm also had greater improvements on the ABC Hyperactivity, Inappropriate Speech, and Stereotypic Behavior (but not other subscales) than did children receiving placebo (p values <0.05, effect sizes of 0.4 to 0.6). Scores on the Children's Social Behavior Questionnaire did not differ between groups. Response inhibition (as measured using a go-no go task) improved significantly in the atomoxetine group versus placebo but distractibility did not.[55]

In a 20-week open label extension including 88 children from the 8-week study (42 from the treatment group and 46 from placebo), overall scores on the ADHD Rating Scale improved from the 8-week baseline to the 28 week followup (p=0.015); changes on the inattention subscale were not significant.

An earlier 6-week crossover RCT (moderate risk of bias) including children with ASD and ADHD reported significant improvements in hyperactivity associated with atomoxetine compared with placebo (effect size=0.90, p=0.04), but changes in inattention measures were not significantly different between groups.[100] Investigators considered seven children (43%) to be responders to atomoxetine (25% improvement in ABC-Hyperactivity scale and CGI rating of very much improved or improved).

Table 16. Key outcomes in studies of atomoxetine

Author, year Groups (dose), N enrollment / N final Study Design Treatment duration/Follow-up timepoint post-treatment Risk of Bias	Outcome measure/Baseline scores, mean ±SD	Outcome measure/Post-treatment scores, mean ± SD
Van der Meer 2013[55-58] RCT G1: Atomoxetine (1.2mg/kg/day), 48/43 G2: Placebo (NA), 49/46 8 weeks/EOT Low	ADHD Rating Scale – Total Score G1: 40.7 ± 7.5 G2: 38.6 ± 8.4 ADHD Rating Scale – Inattention G1: 20.7 ± 3.9 G2: 20.6 ± 4.6 ADHD Rating Scale – Hyperactivity/impulsivity G1: 20.0 ± 5.3 G2: 17.9 ± 6.1 CTRS-R:S – Oppositional G1: 4.1 ± 3.5 G2: 3.6 ± 3.5 CTRS-R:S – Hyperactivity G1: 8.8 ± 5.5 G2: 8.2 ± 5.1 CTRS-R:S – Cognitive/Attention G1: 6.8 ± 4.5 G2: 4.8 ± 3.7 CTRS-R:S – ADHD G1: 18.5 ± 9.3 G2: 18.1 ± 7.5 Go/No-Go Task – Proportion false alarms G1: 0.07 ± 0.1 G2: 0.06 ± 0.08 Missed Go Signals – Proportion misses G1: 0.02 ± 0.06 G2: 0.02 ± 0.05 Response Time G1: 532.7 ± 144.9 G2: 485 ± 120.7 Response Time Variability G1: 125.1 ± 64 G2: 120 ± 77.2 ABC – Irritability G1: 17.3 ± 9.1	**EOT (8 wks)** ADHD Rating Scale – Total Score G1: 31.2 (29.2-33.9) G2: 38.3 (36.0-40.5) G1 Vs G2: p<0.001 ADHD Rating Scale – Inattention G1: 17.0 (15.7-18.4) G2: 19.9 (18.7-21.1) G1 Vs G2: p=0.002 ADHD Rating Scale – Hyperactivity/impulsivity G1: 14.2 (12.8-15.7) G2: 18.4 (17.0-19.7) G1 Vs G2: p=0.001 CTRS-R:S – Oppositional G1: 3.2 (2.3 - 4) G2: 3.7 (2.9 – 4.6) G1 Vs G2: p=0.37 CTRS-R:S – Hyperactivity G1: 6.8 (5.5 - 8) G2: 8.8 (7.6 - 10) G1 Vs G2: p=0.024 CTRS-R:S – Cognitive/Attention G1: 5.1 (4.4 – 5.8) G2: 5.8 (5.1 – 6.5) G1 Vs G2: p=0.18 CTRS-R:S – ADHD G1: 15.1 (13 – 17.2) G2: 17.8 (15.7 – 19.8) G1 Vs G2: p=0.077 ABC – Irritability G1: 14.6 G2: 15.6 G1 Vs G2: p=0.452, d=0.2 ABC – Lethargy/Social Withdrawal G1: 11.4 G2: 11.7 G1 Vs G2: p=0.850, d=0.0 ABC – Stereotypic Behavior G1: 3.0 G2: 4.6 G1 Vs G2: p=0.014, d=0.5 ABC – Hyperactivity G1: 21.2 G2: 25.6

	G2: 16.2 ± 9.5 ABC – Lethargy/Social Withdrawal G1: 12.5 ± 8.4 G2: 12.5 ± 8 ABC – Stereotypic Behavior G1: 6.5 ± 5.1 G2: 4.1 ± 4.5 ABC – Hyperactivity G1: 28.4 ± 9.3 G2: 25.4 ± 11.5 ABC – Inappropriate Speech G1: 4.7 ± 3.2 G2: 4.6 ± 3.4 CSBQ – Total Score G1: 53.6 ± 14.8 G2: 53.1 ± 15.7	G1 vs G2: p=0.010, d=0.6 ABC – Inappropriate Speech G1: 3.7 G2: 4.5 G1 Vs G2: p=0.045, d=0.4 CSBQ – Total Score G1: 46.2 G2: 50.1 G1 Vs G2: p=0.069, d=0.4 CGI – Very Much Improved G1: 0 (0) G2: 1 (2.2) CGI – Much Improved G1: 9 (20.9) G2: 3 (6.5) G1 Vs G2: p=ns CGI – Minimally Improved G1: 12 (27.9) G2: 6 (13) CGI – No Change G1: 16 (37.2) G2: 30 (65.2) CGI – Minimally Worse G1: 4 (9.3) G2: 3 (6.5) CGI – Much Worse G1: 2 (4.7) G2: 3 (6.5) CGI – Very Much Worse G1: 0 (0) G2: 0 (0)
Arnold 2006[100] RCT G1: Atomoxetine (up to 1.4mg/kg/day), 16/16 G2: Placebo (1.2 mg/kg/day), 16/16 6 weeks/EOT (crossover) Moderate RoB	ABC – Hyperactivity G1: 24.69 ± 13.08 G2: 22.5 ± 12.87 ABC – Irritability G1: 16 ± 9.28 G2: 14.13 ± 9.89 ABC-Lethargy/social withdrawal G1: 8.69 ± 9.24 G2: 6.62 ± 8.36 ABC – Stereotypic behavior G1: 7.37 ± 6.20 G2: 6.19 ± 5.86 ABC – Inappropriate speech G1: 5.75 ± 3.38 G2: 5.43 ± 3.16 CGI-Severity G1 + G2: 4.69 ± 0.60	**Week 6** ABC – Hyperactivity G1: 19.31 ± 13.42 G2: 22.37 ± 12.89 p=0.04; ES=0.9 ABC – Irritability G1: 13.06 ± 9.28 G2: 14.13 ± 9.89 p=ns; ES=0.61 ABC-Lethargy/social withdrawal G1: 6.50 ± 8 G2: 7.43 ± 9.64 p=0.01; ES=1.18 ABC – Stereotypic behavior G1: 4.69 ± 5.84 G2: 6.63 ± 5.8 p=ns; ES=0.87 ABC – Inappropriate speech G1: 4.87 ± 2.85 G2: 5.43 ± 3.16

	Repetitive behavior scales – Total score G1: 53.12 ± 22.2 G2: 49.06 ± 21.54	p=ns; ES=0.52 CGI-Improvement (1 or 2) G1: 9 (56) G2: 4 (25) Repetitive behavior scales – Total score G1: 43.5 ± 23.94 G2: 45 ± 5.99 p=ns; ES=0.09

ABC = Aberrant Behavior Checklist; CGI = Clinical Global Impressions Scale; CSBQ = Children's Social Behavior Questionnaire; CTRS = Connor's Teacher Rating Scales; EOT = End of Treatment; ES = Effect Size; G = Groups; kg = Kilograms; mg = Milligrams; NA = Not Applicable; NS = Not Significant; RCT = Randomized Controlled Trial; RoB = Risk of Bias; SD = Standard Deviation

Harms of Atomoxetine

During the 8-week treatment versus placebo phase in one RCT, 81.3 percent of children receiving atomoxetine compared with 65.3 percent of placebo participants reported at least one adverse event (p=ns) in one study; one child in the atomoxetine group discontinued due to fatigue.[55-58] Significantly more treatment than placebo participants reported nausea (14 vs. 4), decreased appetite (13 vs. 3), fatigue (11 vs. 3), and early morning awakening (5 vs. 0, all p values <0.05). In the open-label extension phase, 11 of 88 participants withdrew from the study due to adverse effects. Adverse effects occurring in more than 10 percent of participants in the first 8 weeks of treatment included upper abdominal pain (12.5%), decreased appetite (18.2%), fatigue (18.2%), headache (20.5%), and nausea (13.6%). Most harms attenuated over time: during the open label phase, only headache continued to occur in more than 10 percent of participants (14.8%).

In another RCT, more children in the atomoxetine group had gastrointestinal symptoms, fatigue, and racing heart rate (p values <0.05) than did children in the placebo group.[100]Four children receiving placebo had severe adverse events including restlessness, mood swings, decreased appetite; among those receiving atomoxetine severe events included rage requiring hospitalization in one child (leading to study withdrawal) and tiredness in another. Table 17 outlines harms.

Table 17. Harms/adverse effects in studies of atomoxetine

Harm/Adverse Event*	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Atomoxetine		
GI symptoms[55-58, 100]	2 (59/64)	25%-64.6%
Appetite decrease[55-58, 100]	2 (25/64)	27.1%-75%
Challenging behavior[55-58]	2 (16/64)	4.2%-88%
Dizziness[55-58, 100]	1 (3/48)	6.3%
Agitation/nervousness/restlessness[100]	1 (16/16)	100
Dry mouth[100]	1 (4/16)	25%
EPS/impaired movement[100]	1 (7/16)	43.8%
Headache[100]	1 (4/16)	25%
Heart rate changes[100]	1 (4/16)	25%
Insomnia[100]	1 (12/16)	75%
Skin changes[100]	1 (8/16)	67%
Somnolence[100]	1 (12/16)	75%
Placebo		
Appetite decrease[55-58, 100]	2 (11/65)	6.1%-52%

Challenging behavior[55-58, 100]	2 (16/65)	6.1%-81%
EPS/impaired movement[55-58, 100]	2 (11/65)	8.2%-31%
Agitation/nervousness/restlessness[100]	1 (16/16)	100
Dry mouth[100]	1 (4/16)	25%
GI symptoms[100]	1 (14/16)	87.5%
Headache[100]	1 (7/16)	44%
Insomnia[100]	1 (7/16)	44%
Skin changes[100]	1 (6/16)	38%
Somnolence[100]	1 (7/16)	44%

*Harms reported by more than one participant. EPS=extrapyramidal; GI=gastrointestinal; n=number

Studies of Nutritional Supplements or Specialized Diets

Key Points

- Three RCTs compared omega-3 fatty acid supplementation and placebo, and strength of evidence is low for no effect of supplementation on challenging behaviors and low for an association with minimal harms.
- Despite the number of RCTs with low or moderate risk of bias addressing other agents, evidence is insufficient for all clinical efficacy and harms outcomes because few, small, underpowered studies addressed each diet or supplement.
- No conclusions can be reached about the relative effectiveness of the other intervention compared with placebo (insufficient strength of evidence).

Overview of the Literature

We identified 14 RCTs (one reported in two publications) that evaluated the use of supplements or dietary manipulation to treat ASD symptoms.[42, 43, 48, 51, 54, 59, 61, 75-78, 92, 93, 96, 99, 106] Two of these studies[77, 106] were included in our 2011 review. Studies addressed nutritional supplements including omega-3 long-chain free fatty acid (FFA) supplementation,[59, 61, 75, 92] methyl-B12 supplement,[96] digestive enzymes,[77, 78] L-carnitine,[76, 99] and the amino acid derivative N,N-Dimethylglycine.[106] Dietary interventions addressed in studies included gluten-free and casein-free (GFCF) diet,[42, 43, 51] gluten/casein challenge foods,[54, 93] and camels' milk.[48]

Studies were conducted in the United States,[51, 61, 75, 76, 92, 93, 96, 106] Australia,[77] Belgium,[54] Denmark,[42, 43] Egypt,[78, 99] Holland,[59] and Saudi Arabia.[48] Study treatment durations ranged from 7 days to 2 years, and sample sizes ranged from 12 to 101 (total N=669). Followup occurred immediately post-treatment in all studies. Four RCTs had low risk of bias,[51, 92, 93, 96] ten had moderate,[42, 43, 54, 59, 61, 75, 77, 78, 99, 106] and two had high risk.[48, 76] No studies reported industry funding.

Detailed Analysis

Despite the number of RCTs with low or moderate risk of bias addressing supplements or diets, evidence is insufficient to determine their effects on any outcome in the short- or long-term. Most studies were small (median 38 total participants), short-term (ranging from 1 week to 7 months, with 24 months of treatment in one study), and most (4/6; no calculation provided in 10 studies) studies reporting power calculations were not adequately powered to detect effects. We provide brief summaries of reported outcomes by agent below. Appendix F includes summary tables with detailed findings.

Studies of Nutritional Supplements

Free Fatty Acid (Omega-3) Supplementation

Little evidence supports the effectiveness of FFA supplementation to improve core or associated ASD symptoms. Three RCTs of omega-3 FFA versus placebo (low[92] and moderate[59, 75] risk of bias) reported no significant group differences on most measures of challenging behavior, communication, language, and adaptive behavior including the ABC, CGI, Peabody Picture Vocabulary Test, Pervasive Development Disorder Behavioral Inventory (PDD-BI), VABS, Behavior Assessment System for Children (BASC), and Social Responsiveness Scale.[59, 75, 92] One study reported significantly improved scores in the placebo group compared with the omega-3 group on the BASC externalizing problems scale after 6 months of treatment,[59] and another reported significant improvement in parent ratings of stereotypy and lethargy in children receiving omega-3 supplements compared with those receiving placebo, but teacher ratings were not significantly different.[75] Another moderate risk of bias RCT of dietary docosahexanoic acid (DHA) supplementation versus placebo reported improvement in parent-rated social skills on the BASC in children receiving placebo vs. those receiving DHA, while teachers rated communication as more improved in the treatment group compared with placebo.[61] Scores on other measures including the CGI, ABC, and Child Development Inventory did not differ significantly between groups.

Digestive Enzyme Supplementation

Evidence is insufficient to determine if short-term digestive enzyme supplements affect ASD core or associated symptoms. Two RCTs with moderate risk of bias addressed digestive enzyme supplements compared with placebo: one evaluated a proteolytic enzyme supplement (Peptizyde)[77] and the other a digestive enzyme supplement (Neo-Digestin).[78] The Peptizyde RCT reported no significant differences in measures of behavior, sleep quality, or gastrointestinal symptoms, and no significant differences in adverse effects.[77] In a 3-month trial of Neo-Digestin versus placebo, CARS scores improved significantly in the treatment group compared with placebo.[78]

Other Supplements

Methyl B12 and N,N-Dymethylglycine supplementation were addressed in two placebo-controlled RCTs with moderate[106] and high[96] risk of bias. These studies reported few significant group differences in measures of behavior or communication assessed. In two RCTs addressing L-carnitine (moderate[99] and high[76] risk of bias), ASD severity scores improved significantly in the L-Carnitine group compared with placebo in one, but scores on other behavioral measures or measures of adverse effects did not differ between groups.[76] In the second RCT, symptom severity did not differ between groups after 6 months of treatment.[99]

Studies of Dietary Manipulation

Gluten-Free Casein-Free Diets (GFCF)

Data to assess effects of GFCF diets are limited as dietary approaches and outcome measures varied among studies. Two RCTs compared GFCF diets to either an unaltered diet[42, 43] or a diet that contained gluten and dairy.[51] In a small, low risk of bias trial, scores on measures of challenging behavior did not differ between groups after 6 weeks of therapy.[51] Another trial (moderate risk of bias) with 24-month followup of participants reported few differences in

behavioral measures between children on a GFCF diet and those with no dietary restrictions;[42, 43] scores on the Autism Diagnostic Observation Schedule (ADOS) and Gilliam Autism Rating Scale improved significantly in participants in the GFCF group vs. no diet group at 12 months, but scores were not different on any measure in a subset of participants followed for 24 months.

Gluten and Casein Challenge Foods

Two small RCTs (low[107] and moderate[54] risk of bias) evaluated "challenges" of gluten or casein containing foods, but evidence is insufficient to determine if short-term gluten- casein containing foods affect ASD symptoms or gastrointestinal function. One RCT randomized children who were maintaining GFCF diets to foods with gluten, gluten and casein, or placebo foods.[93] The study reported no significant group differences in measures of challenging behaviors or measures of sleep quality and stool frequency at any time point over the 30-week trial. Another RCT assessing effects of introducing gluten-casein containing foods versus placebo foods similarly reported no significant effects on behavior or gastrointestinal symptoms.[54]

Camel Milk

A single RCT (high risk of bias) compared boiled or raw camel's milk with cow's milk and reported no significant differences in ASD severity between groups after 2 weeks of treatment.[48]

Harms of Nutritional or Dietary Interventions

Studies that reported harms either reported no significant difference between the intervention group and the control group, or reported zero harms for each group. Appendix F includes detailed harms tables.

Studies of Risperidone Adjuncts

Key Points

- Though 13 RCTs with low or moderate risk of bias compared risperidone plus an adjunct medication with risperidone plus placebo, few compared the same adjunct agents, and studies thus provide little evidence to inform treatment decisions and can be considered primarily as pilot efficacy trials.
- Most studies reported improvements in irritability with combined treatment compared with placebo plus risperidone, but strength of evidence was insufficient for all comparisons and outcomes given the heterogeneity of agents.

Overview of the Literature

We identified 13 placebo-controlled RCTs addressing risperidone plus an adjunct medication (titrated to 0.5 to 3 mg/day based on body weight).[63-65, 80-89] Two of these studies were included in our 2011 review.[88, 89] Study medications added to risperidone included celecoxib,[82] *Ginkgo biloba*,[86] memantine,[83] topiramate,[65] riluzole,[84] buspirone,[63] N-acetylcysteine,[64, 85] amantadine,[81] pioglitazone,[87] pentoxifylline,[88] galantamine,[80] and piracetam.[89] Studies were short-term (≤ 10 weeks of treatment) with no longer term followup evaluation once treatment ended, and no studies reported industry funding.

Studies included a total of 515 children ranging in age from 3 to 17 years. All studies were conducted in Iran.[63-65, 80-89] We considered 11 studies to have low risk of bias[63-65, 80-87] and two to have moderate risk of bias.[88, 89]

Detailed Analysis

Despite the number of RCTs with low or moderate risk of bias, studies present little evidence to inform treatment decisions and can be considered primarily as pilot efficacy trials. As noted, all studies were short-term and lacked followup past the end of treatment. Studies included few participants (median 40 total/study) and few examined the same adjunct agent or outcomes besides the ABC Irritability subscale. Only two studies[64, 85] addressed the same outcomes with different doses of the same agent (N-Acetylcysteine). All studies except one of *gingko biloba* added to risperidone reported significant improvements on the ABC-Irritability subscale in the adjunct groups compared with placebo plus risperidone; one study reporting only total ABC scores reported significant improvements in the adjunct group compared with placebo.[89] We present a brief summary of key outcomes in each study below; Appendix F includes detailed tables of outcomes and harms. Harms typically did not differ between groups.

N-Acetylcysteine. Two studies[64, 85] compared the effect of different doses of N-Acetylcysteine as an adjunctive therapy to risperidone vs. placebo plus risperidone in a total of 80 children with autistic disorder. By the end of treatment, the N-Acetylcysteine groups had significantly greater reduction in irritability scores ($p<0.035$) than the placebo group in both the trials; in one RCT scores on the hyperactivity/noncompliance ($p<0.05$) subscales were also significantly improved in the N-Acetylcysteine group.[85] Other subscale scores did not differ between groups in either RCT. Adverse events were mild and transient, with a similar incidence in both trials.

Celecoxib. One RCT explored the effectiveness of adding celecoxib as an adjunct to risperidone vs. placebo plus risperidone in 40 children reported significant improvements on the ABC irritability, lethargy/social withdrawal, and stereotypy scales in the adjunct group compared with placebo plus risperidone.[82] Hyperactivity/noncompliance or inappropriate speech did not differ between groups. The frequency of adverse effects as reported by parents was similar between the two groups. By week 10, complete response (50% reduction in irritability subscale) was achieved by 11 of the children in the celecoxib group compared with four (20%) in the placebo group ($p=0.02$).

Ginkgo biloba. In one RCT comparing *Ginkgo biloba* plus risperidone with risperidone plus placebo, investigators found no significant differences between groups on any of the ABC subscales. Side effects were similar between groups.

Memantine. One RCT reported significant reduction in ABC subscale scores for irritability, stereotypic behavior, and hyperactivity in the memantine adjunct group compared with risperidone plus placebo (all $p<0.01$).[83] No significant effects were found on the lethargy or inappropriate speech subscales. Frequency of side effects including extrapyramidal symptoms was similar between the two groups.

Riluzole. In one RCT including children with autistic disorder who responded suboptimally to previous medication, children treated with riluzole and risperidone had significantly greater

improvement in four of the five ABC subscales ($p<0.01$) than those receiving placebo plus risperidone.[84] Based on CGI-I scores, complete response was achieved by 11 children (55%) in the riluzole group compared with five (25%) in the placebo group ($p=0.05$). Among the 16 side effects observed, increased appetite and weight gain were more frequently reported in the riluzole group versus the placebo group ($p \leq 0.03$). All other side effects occurred at a similar frequency in both groups.

Buspirone. More children receiving buspirone plus risperidone had a $\geq$ 30% reduction in irritability score (81.2% vs. 38.9%, $p<0.01$, RR=2.1) than those receiving placebo and risperidone. Investigators reported no serious adverse events in either group, but the odds ratio for increased appetite was 2.61 (61.1% with buspirone vs. 35.3% with placebo). Other commonly reported adverse events were drowsiness (11.1%) and fatigue (11.1%) in the buspirone group and dry mouth (5.9%) by the placebo group.

Topiramate. In one RCT children in the topiramate adjunct group had significantly greater reduction in ABC-C subscale scores for irritability, stereotypic behavior, and hyperactivity/noncompliance (all $p=0.04$) than those receiving placebo.[65] Frequencies of most side effects including extrapyramidal symptoms were similar, though somnolence (35% vs. 5%, $p=0.04$) and decreased appetite (35% vs. 5%, $p=0.04$) occurred more frequently in the topiramate-treated group than the placebo group.

Amantadine. In one RCT including children with severe disruptive symptoms, ABC-Irritability and Hyperactivity/Noncompliance scores were significantly improved in amantadine adjunct group compared with the placebo group ($p \leq 0.03$).[81] By week 10, 17 (85%) of the children in the amantadine group compared with 13 (65%) in the placebo group had partial response (25% reduction in irritability subscale) ($p=0.14$), while complete response (50% reduction in irritability score) was achieved by 7 (35%) vs. 3 (15%) in the amantadine and placebo groups respectively (p=ns). None of the other ABC subscale scores differed between the groups by the end of treatment. Frequency of adverse effects did not differ between groups. Based on the improvement measured by CGI scale, a higher proportion of children in the amantadine group responded to treatment than those in the placebo group (50 % vs. 20%, $p=0.047$), with two and eight children judged to have very much improved and much improved respectively in the amantadine group compared to one and three children in the placebo group.

Pioglitazone. In one RCT children receiving pioglitazone adjunct had significant improvement in the ABC Irritability ($p=0.03$), Lethargy/social withdrawal ($p=0.04$) and Hyperactivity/non-compliance ($p=0.04$) subscale scores compared with the placebo group;[87] scores on other measures did not differ between groups. More children in the adjunct group also had a partial response ($\geq$ 25% reduction in irritability score) than did children receiving placebo (45% vs. 15%, $p=0.04$). Nine children (45%) in the pioglitazone group had complete response ($\geq$ 50% reduction in irritability score) compared with 7 (35%) in the placebo group (p=ns). Adverse events were mild and transient with no group differences in the frequency.

Galantamine. In a trial evaluating galantamine or placebo in addition to risperidone, children in the galantamine adjunct group showed significantly greater improvement in ABC-Irritability ($p=0.017$) and Lethargy/social withdrawal ($p=0.005$) subscales than the placebo group.[80]

Reduction in other ABC subscale scores after treatment was similar between the groups. Sixteen children (80%) in the galantamine group had a complete response (≥ 50% reduction in the irritability subscale score) compared with 10 (50%) in the placebo group (p=0.047), while partial response (≥25% reduction in the ABC-I subscale) was reported in 90% in the galantamine and 65% in the placebo group, p=0.058. The investigators noted no serious adverse events. Both groups reported weight gain by the end of the trial, with no significant group difference.

Pentoxifylline. Scores on the ABC-Irritability, Lethargy/Social Withdrawal, Stereotypic behavior, Hyperactivity/Noncompliance, and Inappropriate Speech subscales were significantly better for the pentoxifylline adjunct group compared with placebo ($p \leq 0.0001$) in one RCT.[88] Frequency of side effects including extrapyramidal symptoms did not differ between groups.

Piracetam: Risperidone plus piracetem was associated with more improvement on the ABC-C total score than risperidone given with placebo in one RCT, with similar incidence of extrapyramidal symptoms and other adverse events.[89]

Studies of Hyperbaric Oxygen Therapy (HBOT)

Key Points

- Studies of HBOT using differing protocols reported conflicting results: no treatment effects in two RCTs and significant improvements in ASD symptoms in another.
- Strength of evidence was insufficient to assess the effects of HBOT compared with placebo on ASD symptoms.

Overview of the Literature

We identified three RCTs with low[45, 52] and moderate[49] risk of bias addressing HBOT compared with a sham treatment. Studies were conducted in the United States[45, 52] and Thailand[49] and included a total of 150 children between 2 and 14 years old. Treatment duration ranged from 20 days to 15 weeks with followup immediately post-treatment. An HBOT manufacturer and the International Hyperbarics Association funded two studies.[45, 52]

Detailed Analysis

Three RCTs of HBOT used different doses and reported inconsistent results (favorable effects associated with treatment in one and no significant effects in two). The RCTs included children with diagnoses of autistic disorder[45, 52] or autism.[49] Two studies used a 24 percent oxygen treatment[45, 52] and a third used 100 percent oxygen;[49] children continued concomitant treatments including behavioral and medical interventions instituted prior to the studies. Two studies of 80[52] or 20[49] hourly treatments reported no significant differences between groups on measures of symptom severity, language, and adaptive behavior (Table 18).[45, 49] In a third RCT including 40 treatment sessions, clinician-rated overall CGI scores, parent-rated language and eye contact measures, the ABC-Irritability subscale, and the Autism Treatment Evaluation Checklist (ATEC) sensory scale improved significantly in the HBOT group compared with the placebo group. Other ABC or ATEC subscale scores did not differ significantly between groups.

Table 18. Key outcomes in studies of hyperbaric oxygen therapy

Author, Year Study Design Groups (Dose), N Enrollment / N Final Treatment Duration/Follow-Up Time Point Post-Treatment Risk of Bias	Outcome Measure/Baseline Scores, Mean ±SD	Outcome Measure/Post-Treatment Scores, Mean ± SD
Sampanthavivat 2012[49] RCT G1: HBOT (20, 1 hr sessions/day at 153kPa), 29/29 G2: Sham air (20, 1 hr sessions/day at 116kPa), 29/29 20 days/EOT Moderate RoB	ATEC-Parent G1: 68.07 ± 25.43 G2: 64.86 ± 22.80 ATEC-Clinician G1: 60.21 ± 19.92 G2: 60.55 ± 21.36 CGIS-Parent G1: 4.03 ± 1.05 G2: 3.79 ± 0.98 CGIS-Clinician G1: 3.62 ± 0.78 G2: 3.83 ± 0.93	**EOT** ATEC-Parent G1: 58.31 ± 21.94 G2: 55.86 ± 24.93 G1 vs G2: p=ns ATEC-Clinician G1: 52.38 ± 19.11 G2: 52.93 ± 18.93 G1 vs G2: p=ns CGIS-Parent G1: 3.69 ± 0.93 G2: 3.66 ± 0.86 CGIS-Clinician G1: 3.48 ± 0.78 G2: 3.76 ± 0.83 G1 vs G2: p=ns Change scores CGIC-Parent G1: 2.34 ± 0.61 G2: 2.55 ± 0.83 G1 vs. G2:p=ns CGIC-Clinician G1: 2.31 ± 0.6 G2: 2.72 ± 0.8 G1 vs G2: p=0.03
Granpeesheh 2010[45] RCT G1: HBOT (24% oxygen at 1.3 atm pressure), 18/17 G2: Placebo (NA), 16/16 15 weeks/EOT Low RoB	SRS NR ADOS NR	**Mean change score:** SRS- Social Awareness G1: -3.14 ± 14.21 G2: -1.33 ± 16.62 G1 vs G2: p=ns SRS-Social Cognition G1: 1.79 ± 8.82 G2: -5.33 ± 16.01 G1 vs G2: p=ns SRS-Social Communication G1: -1.00 ± 13.06 G2: 3.13 ± 12.02

		G1 vs G2:p=ns SRS-Social Motivation G1: -5.50 ± 12.45 G2: -6.33 ± 13.12 G1 vs G2:p=ns SRS-Autistic Mannerisms G1: 1.64 ± 14.58 G2: -3.33 ± 12.49 G1 vs G2: p=0.33 Number (%) improving ADOS-Total G1: 5/18 (27.8) G2: 4/16 (25) G1 vs G2: p=ns ADOS-Communication G1: 3/18 (16.7) G2: 2/16 (12.5) G1 vs G2: p=ns ADOS-Socialization G1: 3/18 (16.7) G2: 2/16 (12.5) G1 vs G2: p=ns
Rossignol 2009[52] RCT G1: HBOT (1.3 atm and 24% oxygen), 33/30 G2: Room air (1.03 atm and 21% oxygen), 29/26 4 weeks/EOT Low RoB	ABC – Irritability G1: 13.2 9.5 G2: 12.2 7.9 ABC – Social Withdrawal/Lethargy G1: 10.5 6.9 G2: 11.2 6.9 ABC – Stereotypic Behavior G1: 7.5 4.9 G2: 6.2 4.7 ABC – Hyperactivity G1: 20.7 9.9 G2: 20.1 8.2 ABC – Inappropriate Speech G1: 3.4 3.1 G2: 3.6 3.6 ATEC – Total Score G1: 75.3 19.5 G2: 75.6 21	ABC – Irritability G1: 10.5 7.4 G2: 11.3 6.4 G1 vs G2: p=0.0976 ABC – Social Withdrawal/Lethargy G1: 9.3 6.7 G2: 8.9 5.6 G1 vs G2: p=ns ABC – Stereotypic Behavior G1: 6.2 5.1 G2: 5.4 4 G1 vs G2: p=ns ABC – Hyperactivity G1: 17.8 9.2 G2: 16.8 7.7 G1 vs G2: p=ns ABC – Inappropriate Speech G1: 2.6 2.5 G2: 3.3 3.2 ATEC – Total Score G1: 65.9 16.4 G2: 70.1 21.9 G1 vs G2: p=ns

		CGI – Improvement (Much or very much improved) G1: 9 (30) G2: 2 (7.7) G1 vs G2: p=0.0471

ABC = Aberrant Behavior Checklist; ADOS - Autism Diagnostic Observation Schedule; ATEC = Autism Treatment Evaluation Checklist; CGI = Clinical Global Impressions Scale; CGIS = Clinical Global Impressions Scale - Severity; EOT = End of Treatment; ES = Effect Size; G = Groups; HBOT = Hyperbaric Oxygen Therapy; kg = Kilograms; mg = Milligrams; NA = Not Applicable; NS = Not Significant; RCT = Randomized Controlled Trial; RoB = Risk of Bias; SD = Standard Deviation; SRS = Social Responsiveness Scale

Harms of HBOT

Studies typically noted that no significant harms occurred. One child had worsening asthma symptoms and discontinued treatment in one study,[52] while 11 children in another experienced middle ear barotrauma that did not lead to discontinuation of the treatment session or the study.[49] Across studies, one child withdrew due to seizures and one due to worsening asthma.

Studies of Other Medical Interventions

Key Points

- Most agents or interventions were addressed in only one study. Those reported in more than one study typically also assessed an adjunct intervention and thus could not be combined.
- While most studies reported some positive treatment effects on sleep, ASD symptoms, or language, strength of evidence was insufficient to assess any comparisons given the heterogeneity of interventions.

Overview of the Literature

We categorized studies as "other" if we could not assess strength of evidence for interventions and outcomes reported (i.e., insufficient strength of evidence) and the studies did not fall under a broader category of intervention such as diet or nutritional supplements. Sixteen studies (14 RCTs, 1 nonrandomized trial, and 1 retrospective cohort study) addressed other medical interventions.[22, 23, 44, 47, 50, 62, 69, 70, 72, 79, 80, 90, 91, 94, 95, 97, 98, 101, 103] Most agents or interventions were addressed in only one study. Those reported in multiple studies included donepezil,[90, 97] and two studies also evaluated melatonin: one comparing it with placebo,[62] and one combining it with behavioral therapy versus each intervention alone.[91]Two studies evaluated bumetanide, one comparing the agent plus applied behavior analysis with behavioral treatment alone,[98] and one comparing bumetanide and placebo.[79]Agents or interventions addressed in single studies included transcranial stimulation (addressed in one multi-publication RCT[69, 70]), amantadine,[72] citalopram,[22, 23] divalproex,[95] stem cell transplantation,[101] oxytocin,[50] mecamylamine,[44] N-acetylcysteine,[94] prednisolone,[103] and tetrahydrobiopterin.[47]

Three studies were included in our prior review,[23, 72, 97] including one RCT that now includes a followup analysis.[22, 23] We considered six studies to have low risk of bias,[22, 23, 44, 47, 91, 94, 95]seven to have moderate risk,[50, 62, 69, 70, 72, 79, 90, 97] and three to have high risk.[98, 101, 103]

No studies reported industry funding. Studies included a total of 778 children (median 39 total children/study) between the ages of 3 and 17 years receiving treatment for 5 days to 14

months. Three studies reported followup after the end of treatment (1-6 months post-treatment).[50, 79, 101]

Detailed Analysis

Despite the number of RCTs with low or moderate risk of bias, studies present little evidence to inform treatment decisions and can be considered primarily as pilot efficacy trials. Most studies were short-term and lacked followup past the end of treatment. Studies included few participants (median 39 total/study) and few examined the same agents. Melatonin and bumetanide were each addressed in two studies, but one study also included an adjunct intervention, so studies cannot be combined. Two studies addressed donepezil but examined different outcomes. Harms reported in studies comparing these interventions were diverse, and their clinical significance is difficult to determine given the short-term nature of the studies and the typically low numbers of participants. Gastrointestinal symptoms including constipation, diarrhea, and abdominal pain occurred frequently as did agitation, nervousness, or restlessness and appetite changes. We present a brief summary of key outcomes in each study below; Appendix F includes detailed tables of outcomes and harms.

Melatonin. Two RCTs evaluated melatonin and reported significant improvements in sleep duration in children receiving combined behavioral therapy and melatonin compared with melatonin alone and improvements in time to fall asleep and sleep time with melatonin versus placebo.[62, 91] One 12-week RCT with low risk of bias compared cognitive behavioral therapy (CBT) alone, melatonin alone, CBT plus melatonin, and placebo in 160 children.[91] CBT consisted of four 50-minute sessions focused on recognizing dysfunctional attitudes about sleep, parent-management of children's sleep, and replacing poor sleep habits with appropriate behavior. All active treatment groups improved in most measures of sleep quality compared with the control group ($p<0.01$). In general, the combination group improved more than the others, followed by melatonin, and CBT. Scores for children who received melatonin alone improved on bedtime resistance, sleep onset delay, sleep duration, and night waking compared with the CBT group ($p<0.001$). Effect sizes ranged from medium to high. Sleep onset latency (time to fall asleep) and sleep efficiency (ratio of total sleep time to total time in bed) were reduced by 50 percent (sleep latency) or 85 percent (efficiency) in 85 and 63 percent of children in the combination group and 39 and 46 percent of children in the melatonin group, respectively. In the CBT arm, 10 percent of children met each criterion, and no children in the control arm achieved these percentages of reduced latency or improved efficiency.

A crossover RCT with moderate risk of bias compared melatonin or placebo for 3 months followed by a 1-month washout and 3 months of either melatonin or placebo.[62] Sleep latency and total sleep were significantly reduced in the melatonin group compared with placebo ($p\leq .004$), but night wakings did not differ between groups. Similarly, scores on the dysomnia scale of the Sleep Difficulties Questionnaire, but not the other sub-scales, were significantly lower for the treatment group compared with placebo ($p=.041$). Scores on the Developmental Behavior Checklist were significantly different between groups (mean difference=6.0, $p=0.05$), with lower scores (improved behavior) in the melatonin group.

Donepezil. Two RCTs (moderate risk of bias) of donepezil assessed differing outcomes and reported no effects on executive function and treatment-associated improvements in language. In an RCT comparing donepezil and placebo, changes between groups on measures of executive

function did not differ significantly after 10 weeks of treatment, though each group generally improved on each measure over time.[90] In a 10-week open label extension, participants generally improved slightly on most measures (differences between baseline and 5 mg or 10 mg doses not significant). Scores on verbal and non-verbal problem solving skills and flexibility of thinking worsened over time (baseline vs. 10-mg dose, $p \leq 0.004$). In another crossover RCT addressed in our prior review,[11] children receiving donepezil versus placebo improved on clinician-rated measures of receptive and expressive language and symptom severity after 6 weeks of treatment (p values <0.05).[97]

Bumetanide. Two RCTs evaluated the diuretic bumetanide, one combining it with behavioral treatment, and reported short-term positive effects on symptom severity. One RCT with moderate risk of bias compared bumetanide or placebo for 3 months followed by repeat evaluations 1 month after the end of treatment.[79] After the 3 month treatment period, CARS scores for participants in the treatment group declined from the severe range to medium or mild severity. At the 120 day followup, scores had shifted back toward pre-treatment values in both groups (p=ns). CGI scores were significantly improved in the treatment group compared with placebo at 120 days (p=0.02), but ADOS total scores did not differ between groups. In analyses removing children with the most severe symptoms, ADOS scores improved significantly in the treatment group (p=0.03). In another high risk of bias, 12-week RCT comparing bumetanide plus daily applied behavior analysis and applied behavior analysis alone, children in the combination arm had significantly improved ABC, CARS, and CGI scores (p values <0.05).[98]

Citalopram. One RCT (reported in multiple publications) addressed the serotonin reuptake inhibitor citalopram and reported no significant effects on repetitive behavior and some positive effects on challenging behaviors compared with placebo.[22, 23] The original study was included in our 2011 review and now includes a followup study examining potential predictors of response to citalopram (see KQ2).[22, 23] The study (low risk of bias) focused on repetitive behavior outcomes in children with PDD and significant repetitive behavior. Investigators reported no significant differences between citalopram and placebo arms on measures of repetitive behavior, with similar baseline scores on the CYBOCS-PDD version and similar improvements in each arm. The other measures of repetitive behavior, including the Repetitive Behavior Scale-Revised, also had similar improvements in each arm with no evidence for an effect of citalopram. The CGI-Improvement scale similarly showed no significant difference between the citalopram and the placebo arm. On the other hand, the primary measure of challenging behavior reported in this trial, the ABC-Irritability subscale, showed an advantage for citalopram with more improvement in the citalopram arm than for placebo.

Mecamylamine. One low risk of bias, 14-week RCT randomized children to either mecamylamine in ascending doses (up to a maximum 5 mg/day) or placebo and reported no significant differences between groups on any of the outcome measures.[44]

N-Acetylcysteine. In a 12-week RCT (low risk of bias) comparing the utility of *n*-Acetylcysteine with placebo, children treated with N-Acetylcysteine had significant improvement on the ABC-Irritability subscale as compared with placebo-treated children (p<0.001);[94] but effects on other behavioral and social measures did not differ.

Amantadine. One moderate risk of bias RCT of amantadine reported no significant effect of daily amantadine over 4 weeks on parent-rated ABC behavior scores and clinician-rated CGI rating of overall improvement compared with placebo.[72] However, children in the amantadine arm improved significantly more than those receiving placebo in clinician-rated ABC Hyperactivity and Inappropriate Speech subscales.

Oxytocin. One RCT with moderate risk of bias including 38 boys with IQs of at least 80 and comorbid ADHD, oppositional defiant disorder, or anxiety compared four doses of nasal oxytocin or placebo over 5 days.[50] Children also received an emotion recognition training program and completed family interaction tasks both before and after oxytocin administration. No outcomes (social interaction, repetitive behavior, emotion recognition, ASD severity) differed between groups on blinded investigator-, parent-, and observation coder-ratings.

Tetrahydrobiopterin. In one 16-week RCT (low risk of bias) comparing tetrahydrobiopterin and including children with Vineland developmental quotients of at least 50, children in the treatment arm had better language, adaptive behavior, and social interaction skills at baseline compared with placebo participants.[47]At followup immediately post-treatment, scores on the primary outcome, the CGI, were not significantly different between groups. Secondary outcomes favored the treatment group: children in the treatment group improved significantly more on the ABC Irritability, Lethargy, Stereotypy, Hyperactive and Inappropriate Speech scales; Social Responsiveness Scale (SRS) total and subscale scores; and VABS composite and subscale measures than did children in the placebo group (p values <0.00).

Divalproex sodium. In a 12-week RCT with low risk of bias including children with ASD and significant irritability or aggression, children receiving divalproex had greater improvements in the CGI-Irritability and ABC-Irritability scales (p values <0.05), but scores on measures of aggression and repetitive behavior (Overt Aggression Scale-Irritability, CYBOCS) did not differ between groups.[95] In exploratory analyses changes in adaptive behavior or manic symptoms also did not differ between groups.

Prednisolone. In one retrospective study (high risk of bias) including children considered to have "regressive" autism (defined as clinically determined loss of age-appropriate language, communication, cognitive abilities and behavior), children who received prednisolone (mean treatment duration of 9.13±3.26 months, range=4-14 months) improved significantly more on a parent- and clinician-rated measure of receptive and expressive language developed for the study.[103] In followup of treated participants approximately 12 months after the end of treatment, participants with improved language (n=17) maintained or increased their improvements; three non-responders continued to have no change in language in parent reports.

Stem cell transplantation. In one 24-week nonrandomized trial (high risk of bias) including 37 children received either rehabilitation therapy plus umbilical cord blood cell transplant, rehabilitation therapy plus stem cell transplant (4 intravenous or intrathecal transplants at 5-7 day intervals), or rehabilitation therapy alone.[101] All children also received sensory integration and behavioral treatment. Symptom severity improved over time in all groups, with significantly greater improvements in the stem cell group compared with each of the other arms (p<0.05). CGI and total ABC scores also improved more in the stem cell group compared with the other groups.

Lethargy/social withdrawal and stereotypy scales improved significantly more in the stem cell group compared with the other arms ($p<0.05$), but scores on the other individual ABC scales did not differ significantly.

Transcranial stimulation. One RCT with moderate risk of bias assessed transcranial direct current stimulation using electrodes attached to the scalp to provide positive and negative electrical currents to putatively affect activity in regions of the brain that may play a role in ASD symptoms.[69, 70] Investigators allocated study participants (all males) with mild to moderate ASD to either active stimulation (2 sessions of roughly 20 minutes) or sham simulation. At 7 days post-treatment, mean clinician-rated CARS scores and parent-rated ATEC total, social, sensory, and health and behavioral problem (but not language) scores were significantly improved in the treatment group compared with placebo (p values <0.05) Scores on the clinician-rated CGAS were also more improved in the treatment group ($p<0.05$) but CGI-Severity scores did not differ between groups. Investigators rated 45 percent of children receiving active treatment and 15 percent receiving sham treatment as "much improved" ($p<0.05$) and 10 percent in each arm as "much worse" (p=NS).

KQ2. Modifiers of Treatment Outcomes

Understanding the degree to which child characteristics (i.e., age, specific ASD-related difficulties and skills), treatment factors (e.g., type, duration, intensity), and systems (e.g., family, community) influence response to treatments could improve targeting of treatments to the appropriate children and circumstances. While we sought modifying effects of child, provider, or intervention characteristics, few studies reported modifiers, and few were likely adequately powered to detect effects. We report modifying variables addressed in studies meeting our criteria as an indication of potential characteristics that may affect findings.

Antipsychotics

A sub-analysis of an 8-week RCT of risperidone vs. placebo[34] analyzed mediators and moderators of the decrease in irritability.[29] Baseline ABC-Irritability subscale score severity was the only significant moderator found. High severity was associated with greater improvement in irritability than was low severity in improvement with risperidone. Weight gain was the only significant mediator of response to risperidone. Greater weight gain was associated with less irritability improvement in the risperidone group. In an analysis of dose and compliance, better compliance was found to be associated with more improvement in the risperidone group and greater dose was associated with greater improvement.

In another post-hoc analysis of data from an extension of the 8-week trial of risperidone, younger age and better communication skills were associated with greater gains in communication but not with gains in daily living skills or socialization as measured on the VABS.[37] No child characteristics were associated with gains in adaptive behavior and gains in each domain of adaptive behavior (e.g., communication, socialization) appeared to contribute equally to gains in the overall adaptive behavior score. Reductions in aggression were also not associated with the magnitude of gains in adaptive behavior.

In secondary analyses of one RCT comparing aripiprazole and placebo, Caucasian children receiving aripiprazole had a relapse rate of 25.8 percent compared with 60.7 percent in the placebo group (HR=0.33, 95% CI: 0.14 to 0.78, p=0.01). Among non-white patients, the difference was not statistically significant. Age also did not interact significantly with relapse.[46]

Finally, in one retrospective cohort study primarily assessing BMI change in children taking either risperidone or aripiprazole, investigators found no variables (baseline BMI or age, race, gender, intellectual disability, concomitant drug use, treatment duration) to be significant covariates of BMI Z-score change per year of treatment.[102]

Stimulants

In a double-blind cross-over trial of MPH in 66 children,[24-27] authors found no effect of age, IQ, weight, or diagnosis on teacher- or parent-rated hyperactivity subscale scores, Swanson Nolan and Pelham rating scale (SNAP-IV), or CYBOCS-PDD scores. Children with Asperger syndrome/PDD-NOS (n=19) showed a trend of being more likely to be classified as responders to both placebo and MPH than those with autism. Response to each dose of MPH was significantly superior to placebo in the autism subgroup but not for the Asperger / PDD-NOS subgroup. In a later analysis assessing gene variants potentially associated with response, variations in seven genes (*SLC6A4, SLC6A3, DRD1, DRD3, DRD4, COMT* and *ADRA2A*) that influence monoaminergic signaling were significant predictors, though the study was not powered to correct for multiple comparisons.[24] In another RCT comparing guanfacine and placebo, cognitive skills were not significantly associated with treatment effects.[66]

Other Agents

Studies of other agents reported various potential modifiers of effects: Response to placebo (but not citalopram) was predicted by severity of disruptive behaviors, particularly hyperactivity, ASD severity and mood, and caregiver strain (p values $\leq$.012) in one study.[22, 23] Children with higher baseline scores on these measures exhibited less response to placebo. In a trial of atomoxetine, scores on tests of inhibition control (go-no go task) and degree of distractibility by irrelevant information (focused-attention task) were not significantly correlated and did not correlate with changes in measures of ADHD symptoms.[55-58]

In a trial of divalproex, analyses suggested that children with abnormal epileptiform electroencephalogram (EEG) results were more likely to respond to divalproex than those with normal EEGs.[95] In analyses of treated children in this trial (n=16), children with higher blood levels of valproate (87-100 mcg/ml) had a better response rate, and higher dose was associated with a moderate effect on improvement scores (p values=NR).

In one RCT comparing HBOT and sham treatment, older age (> 5 years) and lower baseline symptom severity as measured on the ADOS were associated with better outcomes.[52]
An RCT comparing active and sham transcranial stimulation reported that increased left frontal lobe activity as indicated by increases in peak alpha frequencies was associated with improvements in ATEC measures of social problems and health and behavior problems.[69, 70]

None of the included trials of diet or supplement interventions or risperidone adjuncts reported modifiers of effectiveness. The majority of outcomes were not significantly different between the intervention and the comparator groups in diet and nutrition trials.

KQ3. Time to Effect of Interventions

Information about early response to treatment, or lack thereof, could guide treatment selection, implementation, and modification; however, no studies reported data to assess time to effect of interventions. While several studies reported changes in the number of children responding to a given agent over time, studies did not provide data to determine the initiation of effects. One study of aripiprazole noted that clinically important improvements were seen within

8 weeks of treatment, but treatment was not associated with delayed relapse (return of significant symptoms by 16 weeks of treatment/placebo) compared with placebo.[46] Another study assessing transcranial stimulation reported changes in peak alpha frequency immediately post-treatment in children receiving active versus sham stimulation (significant change from baseline in active treatment group and significant between group differences at some electrode sites), but the clinical effects of such changes are not clear.[69, 70]

KQ4. Evidence that Effects Measured at the End of Treatment Predict Long-Term Functional Outcomes

Few studies provided data to address this KQ. Few studies had longer-term followup and those with more than 6 months of treatment or followup typically did not report functional outcomes. In one study, risperidone use was not associated with changes in IQ.[28] Changes from baseline to the end of study in class assignment (e.g., special education, regular classroom) were not significant.

KQ5. Effectiveness Across Environments or Contexts

Five studies reported teacher ratings of outcome measures that provide some information to address this KQ, but the limited results preclude conclusions. One RCT of omega-3 fatty acids reported no significant group differences in teacher ratings of challenging behaviors (parents also rated few measures as improved),[75] while another RCT of DHA supplementation versus placebo reported improvement in parent-rated social skills in children receiving placebo vs. those receiving DHA, while teachers rated communication as more improved in the treatment group compared with placebo.[61] RCTs of methylphenidate reported general agreement between parent and teacher ratings of hyperactivity.[24-27, 53] In one RCT, both parents and teachers considered hyperactivity and impulsive behavior to be significantly improved in the treatment group compared with placebo, but teachers (vs. parents) reported no significant group differences in inattention or oppositional behavior. Finally, an RCT of atomoxetine reported significant teacher-rated improvements in hyperactivity in the atomoxetine group compared with placebo but teacher ratings of cognitive problems/inattention, oppositional behavior, or overall ADHD symptoms did not differ between groups.[55-58]

KQ6. Drivers of Treatment Outcomes

We did not identify studies that provided data to address this KQ.

Discussion

State of the Literature

We identified a total of 60 unique comparative studies, primarily (n=57) randomized controlled trials [RCTs], addressing medical interventions. Most studies were small (median 40 total participants/study) and addressed variable agents. Most studies had placebo comparators, while four (reported in multiple publications) compared a pharmaceutical agent to behavioral treatment or combined pharmaceutical and behavioral treatment.[38-40, 91, 98, 101] Treatment length varied from four days to 24 months, with relatively few studies (n=3) reporting longer term followup after the immediate intervention period.[50, 79, 101]

The methodologic rigor of studies increased substantially over those studies reported in our 2011 review of therapies for children with Autism Spectrum Disorder (ASD).[11] Thirty-three studies in the current review have low risk of bias and 20 have moderate risk. While studies were generally well-conducted, evidence remains insufficient for most interventions given small sample sizes, lack of longer term followup, and heterogeneous agents and populations. While most studies targeted challenging behaviors, only four (reported in multiple publications) explicitly included children with diagnosed comorbidities such as Attention Deficit Hyperactivity Disorder (ADHD).[50, 55-58, 75, 100] Twenty-eight studies used variable criteria to define challenging behaviors, including specific cut-off scores on subscales of the Aberrant Behavior Checklist (ABC); parent-reported irritability; clinician observations of irritability or hyperactivity; or the presence of undefined "severe" behavioral symptoms. Other studies reported no specific indications.

Despite the limitations of the literature, some interventions have high strength of evidence. Specifically, the strength of evidence for the antipsychotics risperidone and aripiprazole is high for the amelioration of irritability in the short term (≤ 6 months of treatment) for children with significant challenging behaviors at baseline. However, the strength of evidence is also high for significant side effects (e.g. extrapyramidal symptoms, weight gain). Longer term effectiveness is not as well studied, but uncontrolled open-label analyses have suggested some continued efficacy. In studies (reported in multiple publications), children receiving the psychostimulant methylphenidate had improvements in hyperactivity, but small sample sizes preclude firm conclusions about durability of effects.[24-27, 53] Two studies (in multiple publications) of atomoxetine also reported positive effects on hyperactivity, potentially with fewer adverse effects than methylphenidate.[55-58, 100] Other studies of agents such as adjuncts to risperidone reported some positive effects but studies were small, often underpowered, and typically not replicated. Studies of nutritional supplements or specialized diets reported few positive effects as did studies of hyperbaric oxygen.

Summary of Key Findings and Strength of the Evidence

KQ1. Benefits and Harms of Medical Treatments

Studies of Antipsychotics

Key Findings

Studies of antipsychotics addressed either risperidone or aripiprazole and reported significant improvements in measures of challenging behavior in the short term (< 6 months) in children receiving the medications compared with those receiving placebo. Harms of these agents, including extrapyramidal symptoms and weight gain, were also significant. Studies reporting longer term followup (up to 21 months for risperidone) suggest continued potential efficacy in many children but did not include control groups that would permit stronger conclusions.

Strength of the Evidence

We considered the strength of the evidence to be high for short-term improvements in challenging behaviors associated with risperidone and aripiprazole and high for significant harms associated with these agents (Table 19). We considered the strength of evidence to be low for longer term (> 6 months) behavioral improvements associated with aripiprazole (assessed in one RCT[46] and uncontrolled, open-label extension of an RCT[15]) and low for longer term improvements with risperidone as two studies of at least 6 months duration assessed this agent (including one open label extension with no control arm).[28, 60] As only one small RCT and one retrospective cohort study compared aripiprazole and risperidone and reported usable data, we considered the strength of the evidence insufficient to assess effects on any outcome.[71] Other outcomes (e.g., ASD symptom severity, repetitive behavior, adaptive behavior) were addressed in single studies; thus we considered strength of evidence insufficient for all other intervention/outcome pairs.

Table 19. Strength of evidence for effectiveness of antipsychotics vs. placebo

Intervention/ Outcome Study Design Risk of Bias and Number of Studies (N Total)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Risperidone vs. placebo						

Challenging behavior RCT: 2 low,[34, 73, 74] 1 moderate[67, 68] (N=274)	Low	Consistent	Direct	Imprecise	Undetected	**High SOE for short-term effectiveness of risperidone in improving challenging behavior compared with placebo** Significant improvement in treatment group vs. placebo in 3 RCTs with 6-8 week treatment phases; improvement maintained in 2 RCTs with 6 months of treatment
Challenging behavior RCT: 1 low,[28] 1 moderate[60] (N=94)	Low	Consistent	Direct	Imprecise	Undetected	**Low SOE for effectiveness in the longer term (> 6 months)** Improvement maintained in 1 RCT with 6 months of treatment and in one open label extension with no comparison group with mean 21 months treatment duration
Harms RCT: 2 low,[28, 33, 34, 73, 74] 2 moderate[60, 67, 68] (N=298)	Low	Consistent	Direct	Imprecise	Undetected	**High SOE for significant harms associated with risperidone** Harms including weight gain, appetite changes, drowsiness, fatigue, extrapyramidal symptoms, drooling/hypersalivation, and gastrointestinal symptoms consistently reported
Aripiprazole vs. Placebo						
Challenging behavior RCT: 2 low[20, 21] (N=316)	Low	Consistent	Direct	Precise	Undetected	**High SOE for short-term effectiveness of aripiprazole in improving challenging behavior compared with placebo** Significant improvements in 2 short-term RCTs in treatment groups
Challenging behavior RCT: 2 low[15, 20, 21, 46] (N=415)	Low	Inconsistent	Direct	Precise	Undetected	**Low SOE for longer term effectiveness in improving challenging behaviors** In longer term followup, no differences in time to relapse of symptoms between aripiprazole and placebo groups in one 16 week RCT and continued improvements in ABC in one 52-week open label continuation with no control arm

Harms RCT: 3 low,[18, 20, 21, 46, 108] (N=415)	Low	Consistent	Direct	Precise	Undetected	**High SOE for significant harms associated with aripiprazole** Harms including weight gain, appetite changes, somnolence, extrapyramidal symptoms, drooling/hypersalivation, infection, and gastrointestinal symptoms consistently reported

N = Number; RCT = Randomized Controlled Trial; SOE = Strength of Evidence

Studies of Stimulants

Key Findings

Studies of methylphenidate (MPH) and guanfacine both reported improvements in hyperactivity and other challenging behaviors with treatment compared with placebo. Significant side effects were associated with MPH including aggressive behavior and appetite changes.

Strength of the Evidence

Methylphenidate. Strength of evidence for effects on hyperactivity was low as studies were small and short term (Table 20). Strength of evidence was also low for no effect on oppositional behavior and low for association with significant harms given the small sample size. These two small studies also reported on changes in social communication with inconsistent results (significant improvements over placebo in one crossover RCT[26] and no group differences in another[53]). Both RCTs had short-term followup and few participants; thus, we considered the evidence insufficient to comment on potential effects on social communication.

Guanfacine. One RCT reported **i**mprovements in hyperactivity, impulsiveness, and attention, but strength of evidence was insufficient given the small sample size and short-term assessment (8 weeks of treatment with immediate followup).[66]

Table 20. Strength of evidence for effects of stimulants

Intervention/ Outcome **Study Design** **Risk of Bias and Number of Studies (N Total)**	**Study Limitations**	**Consistency**	**Directness**	**Precision**	**Reporting Bias**	**Finding** **Strength of Evidence Grade**
MPH vs. Placebo						

Hyperactivity RCT: 2 low[24-27, 53] (N=90)	**Medium**	**Consistent**	**Direct**	**Imprecise**	**Undetected**	**Low SOE for improvements in hyperactivity with MPH compared with placebo** Significant improvement with MPH compared with placebo on parent and teacher-rated measures; differential effect of dose not clear (little effect on 1 study and linear effect in another); SOE is low given small sample size and lack of long-term followup
Oppositional behavior RCT: 2 low[24-27, 53] (N=90)	**Medium**	**Inconsistent**	**Direct**	**Imprecise**	**Undetected**	**Low SOE for no effect of MPH on oppositional behavior** Significant improvement with MPH on parent-rated measure at medium dose level only in 1 RCT; no differences on teacher-rated measures. No differences in teacher-, parent-, or clinician-rated measures in another RCT
Harms RCT: 2 low[24-27, 53] (N=90)	**Medium**	**Consistent**	**Direct**	**Imprecise**	**Undetected**	**Low SOE for association of MPH with significant harms** Rates of children experiencing harms ranged from 0-75%; higher rates reported for repetitive behaviors or speech, loss of appetite, and irritability. Irritability responsible for withdrawals (n=6) in one RCT; SOE is low given small sample size

MPH = Methylphenidate; N = Number; RCT = Randomized Controlled Trial; SOE = Strength of Evidence

Studies of Norepinephrine Reuptake Inhibitors

Key Findings

RCTs addressing atomoxetine reported significant treatment-related improvements compared with placebo that were maintained over 20 weeks of open label, uncontrolled treatment in one study; inattention was significantly improved in one study, and side effects were generally moderate.[55-58, 100]

Strength of the Evidence

Strength of the evidence was low for short-term positive effects of atomoxetine compared with placebo on hyperactivity (Table 21). Strength of the evidence for longer term effect is insufficient as only one study reported a longer duration treatment (with continued reductions in hyperactivity in an uncontrolled 20-week extension). Strength of the evidence was insufficient for effects on inattention as studies reported inconsistent findings.

Table 21. Strength of evidence for effects of atomoxetine

Intervention/ Outcome Study Design Risk of Bias and Number of Studies (N Total)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Atomoxetine vs. Placebo						
Hyperactivity RCT: 1 low, 1 moderate[56, 57, 58:3288, 100] (N=113)	**Medium**	**Consistent**	**Direct**	**Imprecise**	**Undetected**	**Low SOE for improvements in hyperactivity in the short-term (≤ 3 months) with atomoxetine vs. placebo** Significant improvements in rating of hyperactivity in treatment group compared with placebo in both studies
Harms RCT: 1 low, 1 moderate[56, 57, 58:3288, 100] (N=113)	**Medium**	**Consistent**	**Direct**	**Imprecise**	**Undetected**	**Low SOE for moderate harms associated with atomoxetine** No serious adverse events reported in 2 studies; most harms attenuated over open label extension phase

N = Number; RCT = Randomized Controlled Trial; SOE = Strength of Evidence

Studies of Nutritional Supplements and Dietary Interventions

Key Findings

Three RCTs comparing omega-3 fatty acid supplementation with placebo reported no significant group differences in measures of challenging behavior; these studies did not consistently assess language and adaptive behavior outcomes, and no study reported clinically significant harms. Despite the number of RCTs with low or moderate risk of bias addressing other supplements or diets, evidence is insufficient to determine their effects on any outcome in the short- or long-term. Most studies were small and short-term (ranging from 1 week to 7 months, with 24 months of treatment in one study), and most (4/6; no calculation provided in 9 studies) studies reporting power calculations were not adequately powered to detect effects.

Strength of the Evidence

Strength of evidence was low for no effect of omega-3 supplementation on challenging behaviors, low for a lack of associated harms (Table 22), and insufficient to assess effects on language and adaptive behavior. Strength of the evidence was insufficient for all other comparisons and outcomes addressed as few studies addressed the same agents, comparators, or outcomes.

Table 22. Strength of evidence for effects of omega-3 supplementation

Intervention/ Outcome Study Design Risk of Bias and Number of Studies (N Total)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Omega-3 fatty acids vs. Placebo						
Challenging behaviors RCT: 1 low,[92] 2 moderate[59, 75] N=119	**Medium**	**Consistent**	**Direct**	**Imprecise**	**Undetected**	**Low SOE for no effect on challenging behavior** No significant differences between groups in three small, short-term RCTs
Harms RCT: 1 low,[92] 2 moderate[59, 75] N=119	**Medium**	**Consistent**	**Direct**	**Imprecise**	**Undetected**	**Low SOE for lack of significant harms associated with supplementation** No clinically significant harms reported in any study

N = Number; RCT = Randomized Controlled Trial; SOE = Strength of Evidence

Studies of Risperidone Adjuncts

Key Findings

Despite the number of RCTs with low or moderate risk of bias, studies present little evidence to inform treatment decisions and can be considered primarily as pilot efficacy trials. All studies were short-term and lacked followup past the end of treatment. Studies included few participants (median 40 total/study) and few examined the same adjunct agent or outcomes besides the ABC Irritability subscale. Only two studies[64, 85] addressed the same outcomes with different doses of the same agent (N-acetylcysteine). All studies except one of *gingko biloba* added to risperidone reported significant improvements on the ABC-Irritability subscale in the adjunct groups compared with placebo or placebo plus risperidone; one study reporting only total ABC scores reported significant improvements in the adjunct group compared with placebo.[89]

Strength of the Evidence

Strength of the evidence was insufficient to assess effects of risperidone plus adjunctive agents including amantadine, buspirone, celecoxib, memantine, riluzole, *gingko biloba*, pioglitazone, or topiramate on any outcome assessed as no study addressed the same adjunctive agent. Studies were also small (<50 children total) and short-term (8-10 weeks of treatment). While two RCTs addressing risperidone plus N-acetylcysteine reported improvements in irritability with the combination vs. risperidone plus placebo, strength of evidence is insufficient to comment on effects given the small number of participants (n=71 total), high attrition (15% to 30% across groups) and short-term nature (10 weeks each) of the studies.

Studies of Hyperbaric Oxygen Therapy (HBOT)

Key Findings

Three RCTs of HBOT used different doses and reported inconsistent results (favorable effects associated with treatment in only one[52] and no significant effects in two[45, 49]).

Strength of the Evidence

We considered strength of the evidence to be insufficient to assess effects on ASD symptoms and language and low for a lack of harms (Table 23).

Table 23. Strength of evidence for effects of hyperbaric oxygen therapy

Intervention/ Outcome Study Design Risk of Bias and Number of Studies (N Total)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
HBOT vs. Placebo						
Harms RCT: 2 low,[45, 52] 1 moderate[49] (N=150)	**High**	**Consistent**	**Direct**	**Imprecise**	**Undetected**	**Low SOE for lack of significant harms associated with HBOT** No study reported harms considered clinically important

ASD = Autism Spectrum Disorder; HBOT = Hyperbaric Oxygen Therapy; N = Number; RCT = Randomized Controlled Trial; SOE = Strength of Evidence

Other Medical Interventions

Key Findings

Melatonin. Two RCTs[62, 91] evaluated melatonin—one comparing melatonin with and without concomitant cognitive behavioral therapy (CBT)—and reported significant improvements in sleep duration in children receiving combined behavioral therapy and melatonin compared with melatonin alone[91] and improvements in time to fall asleep and sleep time with melatonin versus placebo.[62]

Donepezil. Two RCTs of donepezil assessed differing outcomes and reported no effects on executive function and treatment-associated improvements in language.[11, 90]

Bumetanide. Two RCTs evaluated the diuretic bumetanide; while both reported positive effects on symptom severity, effects across studies cannot be combined as one RCT assessed combined bumetanide and behavioral treatment.[79, 98]

Agents addressed in single studies. Studies of citalopram,[22, 23] N-Acetylcysteine,[94] tetrahydrobiopterin,[47] and divalproex[95] reported positive effects on measures of challenging

behavior associated with treatment compared with placebo. Measures of language or symptom severity improved more in treatment arms versus control arms in studies of prednisolone,[103] transcranial stimulation,[69, 70] and stem cell transplantation.[101] One study of amantadine reported significant improvements in hyperactivity relative to placebo.[72]Studies of oxytocin[50] and mecamylamine[44] reported no significant treatment effects.

Harms reported in studies comparing these interventions were diverse, and their clinical significance is difficult to determine given the short-term nature of the studies and the typically low numbers of participants.

Strength of the Evidence

Strength of the evidence was insufficient for comparisons of amantadine, bumetanide, divalproex, oxytocin, mecamylamine, prednisolone, tetrahydrobiopterin, citalopram, and neurostimulation vs. placebo and also for bumetanide vs. bumetanide plus applied behavior analysis; melatonin with or without CBT; and comparisons of cord blood cell transfusion variants plus recreational therapy on any outcomes as no studies addressed the same agents. Studies also typically included fewer than 60 children and only assessed outcomes in the short term.

KQ2. Modifiers of Treatment Outcomes

Few studies reported modifying characteristics, and no characteristics were consistent modifiers.

KQ3. Time to Effect of Interventions

Few studies reported data to assess time to effect of interventions. One study assessing transcranial stimulation reported changes in peak alpha frequency immediately post-treatment in children receiving active versus sham stimulation (significant change from baseline in active treatment group and significant between group differences at some electrode sites), but the clinical effects of such changes are not clear.[69, 70]

KQ4. Evidence that Effects Measured at the End of Treatment Predict Long-Term Functional Outcomes

Few studies had longer-term followup and those few with 6 months or more of treatment or followup typically did not report functional outcomes.

KQ5. Effectiveness Across Environments or Contexts

Five studies reported teacher ratings of outcome measures that provide some information to address this KQ, but the limited results preclude conclusions.

KQ6. Drivers of Treatment Outcomes

We did not identify studies that provided data to address this KQ.

Findings in Relation to What is Already Known

We identified 16 recent (2010-present) systematic reviews or meta-analyses addressing medical interventions for children with ASD. Three reviews evaluated the antipsychotics

aripiprazole and risperidone; six evaluated multiple agents including antipsychotics; and seven evaluated agents including SSRIs, atomoxetine, gluten-free casein-free diets, omega-3 fatty acids, melatonin, and hyperbaric oxygen.

Overall, findings in these reviews generally aligned with the findings presented here, with high strength of evidence for short-term effectiveness of aripiprazole and risperidone to ameliorate challenging behaviors and high strength of evidence for adverse effects of each agent. Several reviews commented on atomoxetine as a promising agent, and one commented on melatonin to improve sleep problems. Reviews noted little evidence for gluten-free casein-free (GFCF) diets, omega-3 fatty acids, hyperbaric oxygen, antiepileptic medications, selective serotonin reuptake inhibitors (SSRIs), and chelating agents.

Reviews generally considered studies of antipsychotics to have high quality and the quality of studies addressing stimulants and atomoxetine as moderate to high. Reviews generally considered studies addressing nutritional supplements, diets and hyperbaric oxygen as moderate to low quality. Reviews consistently commented on a lack of long term data and typically small sample sizes as limitations of the strength of the evidence.

Antipsychotics

One Cochrane review of aripiprazole included two RCTs and reported significant short-term treatment-related improvements on irritability, hyperactivity, and repetitive movement with weight gain, sedation, drooling, and neurological side effects.[109] Another review including children with ASD (n=637), developmental disorders (n=68), or intellectual disability (n=50) noted that all of the 20 included randomized and observational studies reported significant treatment-related improvements in problem behaviors measured on the CGI or ABC.[110] Most studies reported adverse effects including weight gain, sedation, and tremor. Both reviews noted a need for longer term studies to address durability of effects. One meta-analysis of risperidone (n=608 children) reported a mean effect size for risperidone of 1.09 across studies (1.14 for open label studies and 1.12 for placebo-controlled) using global outcome measures such as the CARS and CGI.[111] The effect size for outcomes related to maladaptive behaviors such as irritability and aggression was 1.20.

Reviews of Multiple Agents

Agents to treat irritability and problem behaviors. One review and meta-analysis addressed treatment of severe irritability and problem behaviors and included 11 RCTs that used the ABC-Irritability subscale in quantitative analyses. The review reported significant treatment effects for aripiprazole (effect size=0.9), risperidone (effect size=0.8), and N-Acetylcysteine (effect size=0.7) compared with placebo.[112] Harms occurring with risperidone and aripiprazole included somnolence or sedation, and extrapyramidal symptoms occurred with aripiprazole and haloperidol. Aripiprazole, risperidone, and valproate caused greater weight gain compared with placebo (effect sizes of 3.1, 0.8, and 0.3, respectively). Investigators also noted smaller effects for clonidine, methylphenidate, tianeptine, venlafaxine, and naltrexone in studies that did not specifically target irritability and that atomoxetine and dextromethorphan were associated with improvements in hyperactivity and impulsivity on the ABC-Hyperactivity subscale.

Psychotropic medications. One review of 17 different medications reported addressed in 33 RCTS reported little established evidence to support any medication.[113] Investigators considered aripiprazole, risperidone, haloperidol to be have established evidence for treating irritability and

hyperactivity (risperidone); irritability, hyperactivity, and stereotypy (aripiprazole); and unspecified behavioral symptoms (haloperidol). The review noted promising evidence for methylphenidate's effects on hyperactivity. Investigators considered evidence preliminary for the effects of risperidone on repetitive behavior and stereotypy, for the effects of atomoxetine and naltrexone on hyperactivity, and for pentoxifylline on irritability and social withdrawal. Investigators reported evidence as insufficient for all other agents (clonidine, guanfacine, olanzapine, divalproex, lamotrigine, levetiracetam, citalopram, fluoxetine, clomipramine, amantadine, naltrexone) on outcomes including social behavior, hyperactivity, and repetitive behavior.

Agents to treat ADHD symptoms. One review identified seven placebo-controlled trials of medications targeting ADHD symptoms in children with Pervasive Development Disorders (n=225 children) and reported that methylphenidate was significantly more effective than placebo in treating ADHD symptoms (effect size 0.67) and hyperactivity specifically (effect size=0.66).[114] Appetite decrease, insomnia, depressive symptoms, irritability, and social withdrawal occurred significantly more frequently in the treatment group versus placebo. The review reported no significant effects for clonidine versus placebo and significant improvements in ADHD symptoms and hyperactivity in children taking atomoxetine compared with placebo. Harms included nausea, decreased appetite, and sleep changes.

Antiepileptic medications. One meta-analysis evaluated valproate, lamotrigine, levetiracetam, and topiramate in children with ASD.[115] In meta-analyses, single agents studied were not significantly different between treatment and placebo arms. One study of topiramate combined with risperidone reported improvements in irritability in the combination group compared with risperidone plus placebo. Two studies of valproate and one of levetiracetam reported no response to treatment as defined by CGI ratings. Discontinuation due to adverse effects did not differ between groups nor did the rate of total adverse events.

Alzheimer's medications. One review addressed use of these medications for children and adults with ASD and included case reports and other observational studies and controlled trials.[116] Drugs assessed in children included donepezil, galantamine, rivastigmine, and memantine. Four uncontrolled and one controlled studies of donepezil reported treatment-associated improvements in ASD symptoms. All three studies of galantamine (2 RCTs and 1 case series) reported positive effects on core and associated ASD symptoms. One small case series addressing rivastigmine reported improvements in expressive language and ASD symptoms, and three studies (1 RCT, 2 case series) of memantine use in children also reported positive effects on irritability and associated symptoms with side effects including gastrointestinal symptoms, worsening behavior, and sedation. The review concluded that evidence is inconsistent and inconclusive but further study of some agents such as rivastigmine may be warranted.

Predictors of placebo response. One meta-analysis included data from 25 RCTs measuring outcomes with either the ABC, CGI, VABS, CARS, or CYBOCS-PDD and reported a moderate but significant placebo response across studies (effect size=0.45, 95% CI: 0.34 to 0.56, $p<0.001$).[117] Investigators identified clinician-completed outcome measures, level of response to active intervention, a pharmacologic active intervention (vs. diet, etc.), use of adjunctive

treatment, and geographical location of the trial (greater response in Iran vs. United States) as significant moderators of the placebo response, with each factor associated with an increased response.

Reviews of Other Agents

Atomoxetine. One review of atomoxetine included six studies (1 RCT) evaluating the agent for treatment of hyperactivity in children with ADHD (n=90).[118] All studies except one (which included children with "severe autistic disorder") reported significant improvements in behavior in parent, teacher, and clinician ratings with treatment. Harms reported included gastrointestinal symptoms, somnolence, irritability, and weight loss; the review concluded that evidence suggests potential efficacy but small sample sizes and short-term studies limit conclusions.

Hyperbaric oxygen therapy. One review including eight studies (2 RCTs) reported little evidence for effects of HBOT in controlled trials, and some promising evidence in small case series.[119] Few studies reported any adverse effects at the pressure levels studied.

SSRIs. One Cochrane review included nine RCTs (5 including only children) evaluating (n=239 children) evaluating the SSRIs fluoxetine, fluvoxamine, fenfluramine, and citalopram.[120] The review reported no evidence for the effectiveness of SSRIs and potential evidence for harms.

Omega-3 fatty acids. One Cochrane review included two RCTs (n=37 children, predominately male with moderate to severe ASD symptoms) evaluating omega-3 fatty acids and reported no evidence for effects on social interaction, communication, hyperactivity, or stereotypy.[121]

GFCF diets. One review included 32 studies, typically with high risk of bias, and noted scarce evidence for GFCF diets, with positive effects reported only in lower quality studies.[122] The review concluded that evidence for the effectiveness or harms of GFCF diets is limited and weak.

Melatonin. One review included 18 studies addressing melatonin for the treatment of sleep problems in ASD.[123] Thirteen observational studies reported improvements in sleep duration, night awakenings, or sleep onset latency, as did five RCTs. Investigators meta-analyzed RCT data and reported significant improvements on these measures with melatonin versus placebo. Harms associated with melatonin included drowsiness, gastrointestinal symptoms, and worsening behavior. No study reported serious adverse events.

Chelation. Though we did not identify studies addressing chelation agents in the current review, one Cochrane review addressed chelation therapy and included one RCT (n=49 children).[124] Investigators considered the study to have high risk of bias and noted that no evidence suggests efficacy for ASD symptoms.

Applicability

By definition, ASD is heterogeneous. Characterizing a "typical" child with an ASD is not possible, although certain symptoms are central to the range of children within the autism spectrum. Individual therapies are developed and tested to ameliorate specific symptoms or groups of symptoms, often in a fairly circumscribed subset of children. Ideally, research on

therapies for ASD should target children most likely to benefit from a particular focus; thus we provide details on the population, intervention, comparator, outcomes, and setting (PICOS) for each interventions addressed in more than one study in Appendix G E to support translation of our findings and assessment of the applicability of each for differing circumstances and children.

Overall, study participants were generally recruited from specialty clinical service programs and represent non-primary care populations. As such, families of these children may be seeking a higher level of care than those of the broader population of children with ASD based upon more severe or acute symptoms, including aggression or other challenging behaviors. Most studies of medical interventions targeted elementary school aged and older children with autism, with little data on the treatment of younger children. Most studies included majority male populations (consistent with the male prevalence of ASD).

Studies also included children with highly variable severity of challenging behaviors, ASD symptom severity, and cognitive impairment. Studies of pharmacological agents often sampled children with high levels of specific symptom patterns (e.g., children with severe challenging behavior at baseline where parents may be willing to pursue pharmacologic intervention and trial participation) who may not reflect the wider population of children with ASD in whom these challenges may not be present. Most of the studies reported including children with at least moderate level of severity of ASD. Studies of stimulants included children with cognitive impairment and with comorbidities including attention deficit hyperactivity disorder, oppositional defiant disorder, and obsessive compulsive disorder. Studies of other approaches had similarly heterogeneous populations. Dietary and nutritional studies included some younger children, with severity of autism not well described or the degree of intellectual functioning not well characterized in most studies. This heterogeneity in population characteristics limits the generalizability of findings to children with differing levels of symptom expression or comorbidities.

Studies addressed a variety of agents and typically reported use of concurrent medications or other therapies. Most agents studied are accessible in the United States albeit with few receiving FDA approval for use. ,. Comparators among non-placebo controlled studies varied, and few studies assessed the effect of concomitant behavioral or other therapies, though many children with ASD receive multiple interventions. The treatments studied may not adequately reflect the broad range of treatment combinations used in the general population of children with ASD. .

As noted, few studies evaluated longer term treatment (> 6 months); short treatment and followup periods limit our ability to understand potential longer term outcomes such as academic achievement or longer term harms. Overall, given the heterogeneity of these studies, and the heterogeneity of children with ASD, it is difficult to generalize findings to the overall population of individuals with ASD. These limitations to generalizability likely reflect both the significant heterogeneity of ASD itself as well as its associated features, such as irritability. Thus, while there is a growing evidence base for treating certain symptoms in certain populations, these findings underscore the continued need for individualized treatment approaches that are informed by the emerging evidence base for benefits as well as harms of medical intervention, with careful consideration of patient symptom presentation and functioning level relative to study populations and applicability of the known literature.

Implications for Clinical and Policy Decisionmaking

This review provides some evidence for decisionmaking about medical interventions for children with ASD. The clearest evidence favors the use of the antipsychotics risperidone and aripiprazole to address challenging behaviors in the short-term (<6 months); however, clinicians and caregivers must balance the significant harms of these agents. The significant side effect profiles make it clear that although these drugs are efficacious, caution is warranted regarding their use in patients without severe impairments or risk of injury. Few studies addressed longer term effects of these agents; thus, our confidence in longer term (> 6 months) effectiveness is low. Studies of adjuncts to risperidone typically reported positive effects on challenging behaviors, but few studies addressed the same agents, precluding our ability to draw conclusions about their effectiveness.

Some evidence supports the use of methylphenidate and atomoxetine for hyperactivity, but only two small, short-term comparative studies addressed each agent, so our confidence in effects is limited. Given that many children with ASD are currently treated with medical interventions, strikingly little evidence exists to support clear benefit for most medical interventions, especially in the realm of interventions such as restrictive diets and supplements. Studies of nutritional supplements or specialized diets were typically underpowered and provided little evidence of effects of these approaches. Several agents were addressed in single studies, which limits conclusions about their effects.

Decisional dilemmas remain regarding characteristics of the child, family, or intervention that may modify effectiveness or predict which children may be most likely to benefit from a given approach. Similarly, the literature base is currently insufficient to inform our understanding of the time to effect of interventions, longer term effectiveness of interventions, generalizability of effects outside the treatment context, effectiveness and applicability to broader ASD populations, and components that may drive effectiveness

Limitations of the Comparative Effectiveness Review Process

We included studies published in English only and did not include unpublished data. We scanned a random sample of 150 non-English abstracts retrieved by our MEDLINE search. Most studies appeared to be case series, narrative reviews, basic science studies, or studies assessing etiology. Only two studies appeared to meet inclusion criteria; thus, given the high percentage of ineligible items in this scan (99%), we concluded that excluding non-English studies would not introduce significant bias into the review. We also included only comparative studies of medical interventions and including at least 10 children with ASD. Given heterogeneity in treatment regimens, outcomes addressed in each study, and patient populations, we were limited in our ability to meta-analyze findings or identify potential subgroups that may respond more favorably to specific treatments. Finally, we used a non-validated tool to assess risk of bias, though we note that the tool evaluates similar constructs to those assessed in tools such as that used by the Cochrane Collaboration, with the addition of ASD-specific domains.

Limitations of the Evidence Base

As noted, studies in the review had small sample sizes and typically limited duration of intervention and followup after intervention, despite significant improvements in study design and execution over time. Populations across studies were heterogeneous in terms of challenging

behaviors, ASD symptom severity, age, and comorbidities. Few studies addressed the same agent and outcomes, and few assessed potential factors that may modify effectiveness or drive effects of interventions. Many (n=53) studies also explicitly noted that concomitant interventions were held steady during the study treatment period; however, few studies reported specific analyses to control for or assess the effects of additional treatments.

Despite these limitations, investigators have made significant improvements in incorporating commonly used measures of symptom severity and behavior to facilitate comparisons across studies. Studies also typically described interventions fully, used standardized diagnostic processes and blinded assessors, and reported on the use or restriction of concomitant interventions.

Research Gaps and Areas for Future Research

Improving research in this area should include methodologic considerations of power and sample size and durability of effects. Sample size and participant followup were frequently insufficient to allow firm conclusions. Duration of treatment and followup were generally short (< 6 months); those studies with longer duration of treatment were open label extensions of RCTs and lacked control arms. Few studies provided data on long-term outcomes after cessation of treatment. Future studies should extend the followup period and assess the degree to which outcomes are durable in "real world" situations.

Another critical area for further research is identifying which children are likely to benefit from particular interventions. To date, studies have provided limited characterization of the subpopulation of children who experience positive response to medical interventions and limited characterization of the extent or type of behavioral challenges children experience at baseline.

Children with ASD also typically receive multiple types of therapies, but few studies addressed combinations of medical and behavioral or other categories of interventions or a medical treatment compared with a non-medical treatment. Few attempted to account for potential effects on ongoing interventions. This not only limited our ability to interpret the effects of medical treatments in isolation but represents a significant gap for families and providers in choosing additional treatments that may bolster (or impair) the effects of behavioral, medication, or other therapies. Few studies (n=9) compared active treatments, and future research to assess comparative effectiveness of antipsychotics and other medications is necessary.

In addition, much of the medical intervention literature relies on baseline and outcome measures that have specific limits in understanding individualized response. Future research attempting to elucidate potential biobehavioral markers of response may prove useful. Research in understanding outcomes of importance to patients and caregivers, such as quality of life, is also lacking.

Harms reporting varied across studies; some studies amply described how harms were tracked, while others listed harms with no indication of how they were assessed (e.g., parent recall, checklist, clinician assessment during followup). This lack of reporting makes comparing harms across studies difficult. For instance, while studies of atomoxetine generally reported fewer harms than did studies of methylphenidate in children with ADHD symptoms, exploring differences in safety profiles is an important area for additional research.

Conclusions

Risperidone and aripiprazole ameliorated challenging behaviors in the short term (< 6 months), but had significant side effects. Methylphenidate and atomoxetine were also associated with improvements in hyperactivity in small, short-term RCTs. Methylphenidate was associated with significant harms (low SOE) while atomoxetine was associated with moderate harms. Omega-3 fatty acid supplementation was not associated with improvements in challenging behaviors or with significant harms. Data on longer term (> 6 months) results and harms of interventions are lacking. Similarly, more research is needed to understand characteristics of the child or treatment that modify outcomes and whether effectiveness of interventions generalizes across different settings such as the home or school. Current evidence also does not inform our understanding of components of interventions that may drive effects. Some therapies hold promise and warrant further study, and the conduct of studies has improved considerably over time (i.e., growing number of randomized controlled trials and use of standardized measures). However, additional studies with larger, well-characterized populations, conducted over longer time frames, and that utilize transparent and rigorous methods to permit comparison across studies, would further inform decisionmaking.

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Acronyms and Abbreviations

ABC	Aberrant Behavior Checklist
ADHD	Attention Deficit Hyperactivity Disorder
ADOS	Autism Diagnostic Observation Schedule
AHRQ	Agency For Healthcare Research And Quality
ASD	Autism Spectrum Disorder
ATEC	Autism Treatment Evaluation Checklist
BASC	Behavior Assessment System for Children
BMI	Body Mass Index
CARS	Childhood Autism Rating Scale
CBT	Cognitive Behavioral Therapy
CER	Comparative Effectiveness Review
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression
CI	Confidence Interval
CYBOCS	Children's Yale-Brown Obsessive Compulsive Scale
DSM-IV	Diagnostic Statistical Manual - IV
EEG	Electroencephalogram
FFA	Free Fatty Acid
GFCF	Gluten Free, Casein Free (Diet)
HBOT	Hyperbaric Oxygen Therapy
IQ	Intelligence Quotient
kg	Kilograms
KQ	Key Question
mg	Milligram
MPH	Methylphenidate
n	Number
NNT	Number needed to treat
NR	Not Reported
ns	Not Significant
ODD	Oppositional Defiant Disorder
OT/SI	Occupational Therapy With Sensory Integration
PDD	Pervasive Developmental Disorder
PDD-BI	Pervasive Development Disorder Behavioral Inventory
PDD-NOS	Pervasive Developmental Disorder – Not Otherwise Specified
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting
RCT	Randomized, Controlled Trial
RUPP	Research Units on Pediatric Psychopharmacology
SNAP-IV	Swanson Nolan and Pelham rating scale
SOE	Strength Of Evidence
SRS	Social Responsiveness Scale
TEP	Technical Experts Panel
VABS	Vineland Adaptive Behavior Scales